STATUS OF END ORGAN DAMAGE IN NEWLY DETECTED HYPERTENSION, HYPERTENSION IN THYROID DISORDERS AND KNOWLEDGE AND AWARENESS OF HYPERTENSION AMONG PHYSICIANS AND PUBLIC

A thesis submitted in fulfillment of the requirements for the award of Doctor of Philosophy

Dr Meenakshi Sundaram Ramachandran, MBBS

Declaration by Meenakshi Sundaram Ramachandran

This thesis is the original work of the author, except where specifically referenced. No part of this thesis has been submitted previously, in any form, to this or any other Institution.

For Faculty of Health and Life Sciences,

De Montfort University,

Leicester, United Kingdom

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ABSTRACT

Hypertension is associated with end organ damage (EOD). Since EOD is a risk factor for cardio- and cerebrovascular complications, it is a major requirement for these to be detected, prevented and treated. A total of 147 consecutive patients with newly-diagnosed essential hypertension and attending the outpatient clinic were included in this study based on a set of inclusion and exclusion criteria (patients with co-morbid illnesses were excluded from the investigation). Among them, 86% (70 male (M) and 56 female (F)) had one or more EODs, an observation which was very close to statistically significance (P=0.054). The presence of one or more EODs in newly-detected hypertension indicates widespread vascular damage which carries the high risk for cardio- and cerebrovascular morbidity and mortality.

Although thyroid dysfunctions exert significant effects on blood pressure (BP), published literature available has revealed contradictory data. Objective of our study was to explore the inter-relationships between selected thyroid dysfunctional status (hyper and hypothyroid) and established biomarkers [thyroid stimulating hormone (TSH) and thyroxine (T4)]; and BP components [specifically Systolic BP (SBP), Diastolic BP (DBP), and Mean Arterial Pressure (MAP), and uniquely SBP:DBP ratio]. We followed rigid criteria in order to select adults with hyperthyroidism (n=71) and hypothyroidism (n=300), together with healthy age-matched controls (n =300), and applied a series of statistical analyses on the datasets acquired. We have observed thyroid dysfunctional status is

associated with elevated BP, and increasing BP is positively-correlated with elevated serum thyroid biomarkers, hyper and hypothyroid disorders should be recognized and treated early in order to avoid critical hazards presented by high BP.

Also, we have studied awareness among public and physicians in managing hypertension. Overall, the levels of knowledge and awareness among both groups are sub-optimal. Hence there is an urgent need for empowerment among both groups to enhance awareness and to bring effective standard of care.

TABLE OF CONTENTS

TABLE OF CONTENTS

List of Figures (page number)

List of Tables (page number)

CHAPTER 1. INTRODUCTION

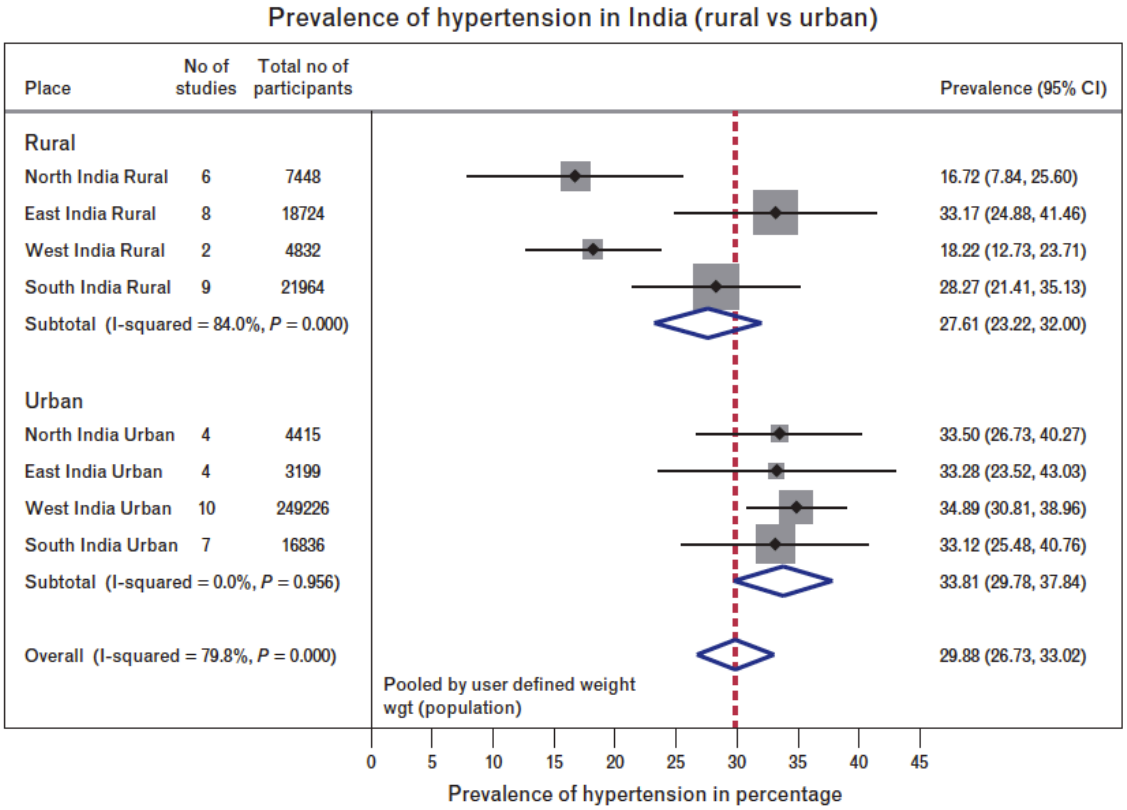
Worldwide, hypertension is the leading risk factor for both morbidity and mortality (1), and represents the attributable burden of disease in South Asia(2). According to the World Health Organization (WHO) Global Health Report 2009, hypertension is the leading cause of mortality (responsible for 13% of deaths globally). Followed by hypertension, tobacco use (9%), diabetes (6%), physical inactivity (6%) and excess weight/obesity (5%) are also responsible for this mortality risk. Indeed, the 2004 WHO report stated that hypertension is one of the important causes for death worldwide (3). Moreover, such conditions affect all groups regardless of their socio-economic status, which was found to be similar in our previous study(4).

By definition, hypertension is defined as a blood pressure index of greater than 135/85 mmHg for automated office/home/ambulatory day-time blood pressure readings, or more than 130/80 mmHg in for 24 hour ambulatory blood pressure readings(5). Patients are considered to be hypertensive even in the first visit if they present with hypertensive urgency or emergency(5). The average blood pressure >160/100 mmHg across 3 visits or average values >140/90 mmHg across 5 visits is also acknowledged to indicate hypertension(5). Hypertensive urgencies and emergencies are defined as diastolic blood pressure values ≥ 130 mmHg, or severe blood pressure with end organ damage(5).

The prevalence of hypertension in the Indian population is increasing, and notably it was 25% according to a previous report (6). Different studies showed the rise in prevalence of

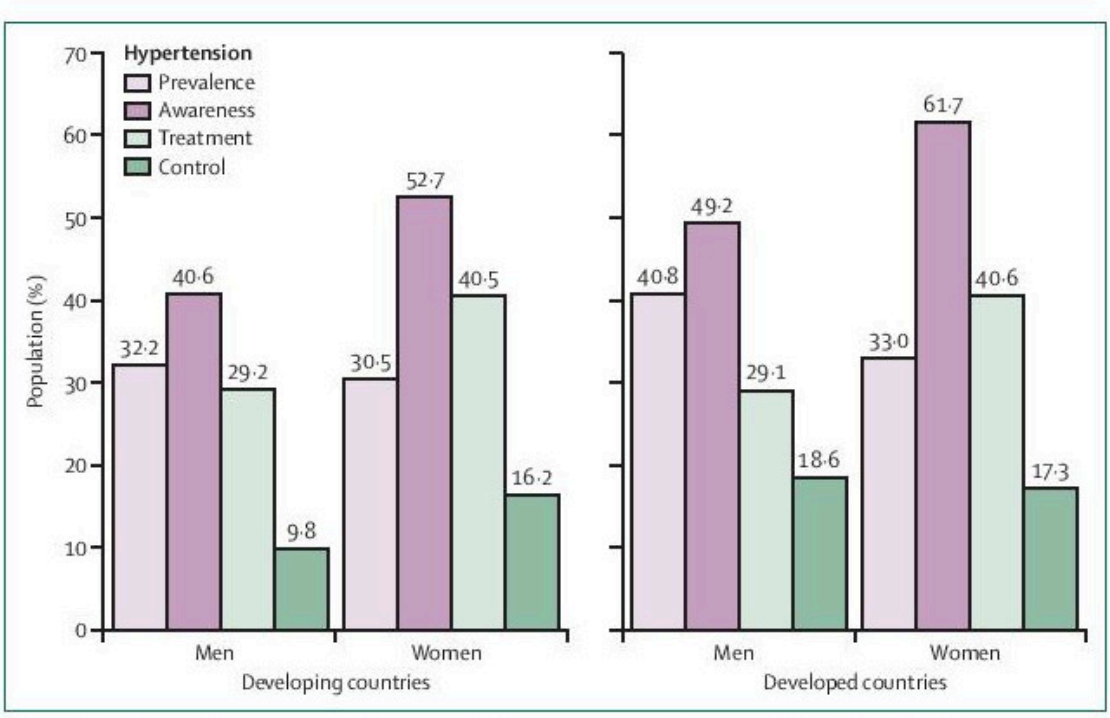
hypertension, however there were some differences noted in the prevalence rate from multiple reports. In the 2005 worldwide analysis of data available for the global burden of hypertension, the prevalence of hypertension amongst Indian men and women were 20.6% and 20.9%, respectively(7). These rates amongst Indian men and women are expected to go up to 22.9 and 23.6 % by 2025, respectively (7). The prevalence amongst urban and rural populations were 25 and 10% respectively (8-11). There was a notable difference in the prevalence and awareness of hypertension amongst the rural and urban Indian populations, and this is depicted in Figure 1.1 (12). From the WHO report of 2008, the prevalence of hypertension amongst Indians was 32.5% (33.2% in men and 31.7% in women)(13). A multi-centre study from India showed that only about 25% of the patients had their blood pressure adequately controlled (14). Ibrahim etal., observed a notable difference in the prevalence, treatment, control and awareness of hypertension between people of developed and developing nations(15). Figure 1.2 illustrates these observations.

Figure 1.1. Overall pooled estimates for the prevalence of hypertension in India



Legend: Location-wise (rural and urban) and region-wise (north, east, west and south). P values obtained for overall rural and urban differences are: for hypertension prevalence in India (0.05*), for hypertension prevalence in East India (0.98), for hypertension prevalence in Northern India (0.07), for hypertension prevalence in Southern India (0.62), and for hypertension prevalence in West India (0.05*). CI – confidence interval, *statistically significant. Figure reproduced from Anchala etal., (12). P values for overall rural and urban population differences for awareness, treatment and under control for hypertension were 0.002*, 0.112 and 0.03*, respectively.

Figure 1.2. Differences in the measures of hypertension between men and women in developing and developed countries.



Legend: Figure reproduced from Ibrahim etal.,(15)

Table 1.1. Changes in the prevalence of hypertension in following countries over time

Countries	Year	Prevalence (%)	Year	Prevalence (%)
India	1988	6.6	2003	36.4
China	1992-94	22.7	1998	24
Tanzania	1987	26.3	1998	39.9
Turkey	2003	28.9	2007	31.7
Sub-saharan Africa	1998	54	2003	78

Legend: % - percentage, Table is adapted from Ibrahim et. al., (15).

Data for the above table 1.1 is calculated for adults aged more than or equal to 55 years, and hypertension is defined as blood pressure > 160/95 mm Hg. Hence, Table 1.1 indicates that there was a rapid change in the prevalence of hypertension from 1988 to 2003 (it is almost 6 times increased over 15 years)(15). Moreover, this figure represents an underestimate of the abundance of hypertensive patients since the dataset collected included only blood pressure values > 160/90 mmHg as those with hypertension. In a recent hypertension study performed within the Indian population by Gupta et. al., it was shown that 55.3% of the population were aware of hypertension (16). Also, treatments available and the adequate control of blood pressure amongst hypertensive populations were 36.5% and 28.2%, respectively (16). Unfortunately, these rates are still sub-optimal (16).

1.1.Rationale and literature review

1.1.A. End organ damage in hypertension

Hypertension is difficult to diagnose since it is asymptomatic, and blood pressure represents a dynamic measure with inherent minute-to-minute variability; moreover, there is currently a widespread application of erroneous techniques leading to inaccurate measurements (17). In 'masked' hypertension, patients have normal blood pressure in the clinician's office, but high blood pressure during daily life, and these are of a high risk for cardiovascular events (18). Hence, 24-hour ambulatory blood pressure measurements offer an improved role for the management of hypertension, including the prediction of cardiovascular events (19). Furthermore, awareness, treatment and control of hypertension, and also techniques available for the measurement of blood pressure amongst health-care professionals remain sub-optimal (20, 21). Hence, hypertension acts as 'silent' killer for many years prior to the time when overt end-organ damage (EOD) is clinically apparent. Most of the patients with essential hypertension are unaware of their disease status, and hence a large number of these subjects have EOD on their first arrival at hospital (22).

The manifestations of EOD include micro and macrovasculature pathology such as stroke, coronary artery disease (CAD)/structural cardiac problems, retinopathy, proteinuria/chronic kidney disease (CKD), and atherosclerotic changes anywhere in the body system. The cost is greater, efficacy and prognosis are lower, for the management of blood pressure in patients with EOD (23). Hence, the early detection and treatment of EOD determines the cardiovascular prognosis in hypertensive patients, and can retard or prevent

further damage (24). A large body of evidence has suggested that microalbuminuria in hypertensives is a predictor of organ damage and cardiovascular events (25). In our previous report, we noted that increased aortic stiffness, left ventricular hypertrophy (LVH) and increased left ventricular (LV) mass were dependent on the duration and severity of hypertension (26). LVH is an independent risk factor for cardiovascular morbidity and mortality in the general population and amongst hypertensives (27). In addition, large epidemiological studies have shown associations between retinopathy and systemic diseases such as hypertension, cardiovascular diseases, diabetes and stroke (28). Also, a relationship between hypertensive retinopathy and blood pressure values (current and past) has been demonstrated (28). Therefore, hypertensive retinopathy, serves as a further sign of EOD and hence a predictor of cardiovascular risk (29).

1.1.A1.Pathogenesis of end organ damage in patients with hypertension

There are a multitude of factors involved in the pathogenesis of end organ damage in addition to pressure overload in hypertension (30, 31). Furthermore, these factors affected the end organs independent of severity of hypertension (30, 31). These factors include the renin-angiotensin- system (RAS), the sympathetic nervous system, and metabolic and inflammatory processes. Stimulation of RAS increases angiotensin levels, which promotes the left ventricle hypertrophy (LVH). Metabolic causes include obesity and high salt consumption, either through hormones or the RAS promotion of end organ damage in hypertensive patients. Hypertension causes endothelial dysfunction and causes the remodeling of both small and large arteries. This, in turn, reduces the elastic nature of vessels, increases stiffness and decreases distensibility. Moreover, stiffness in the aorta

increases the left ventricular overload and impedes the left ventricular function(26). Overall, this leads to plaque formation, stenosis and aneurysm in the vessel and thus cause vasculopathy. Table 1.2 provides a summary of end organ damage experienced in hypertension patients (31).

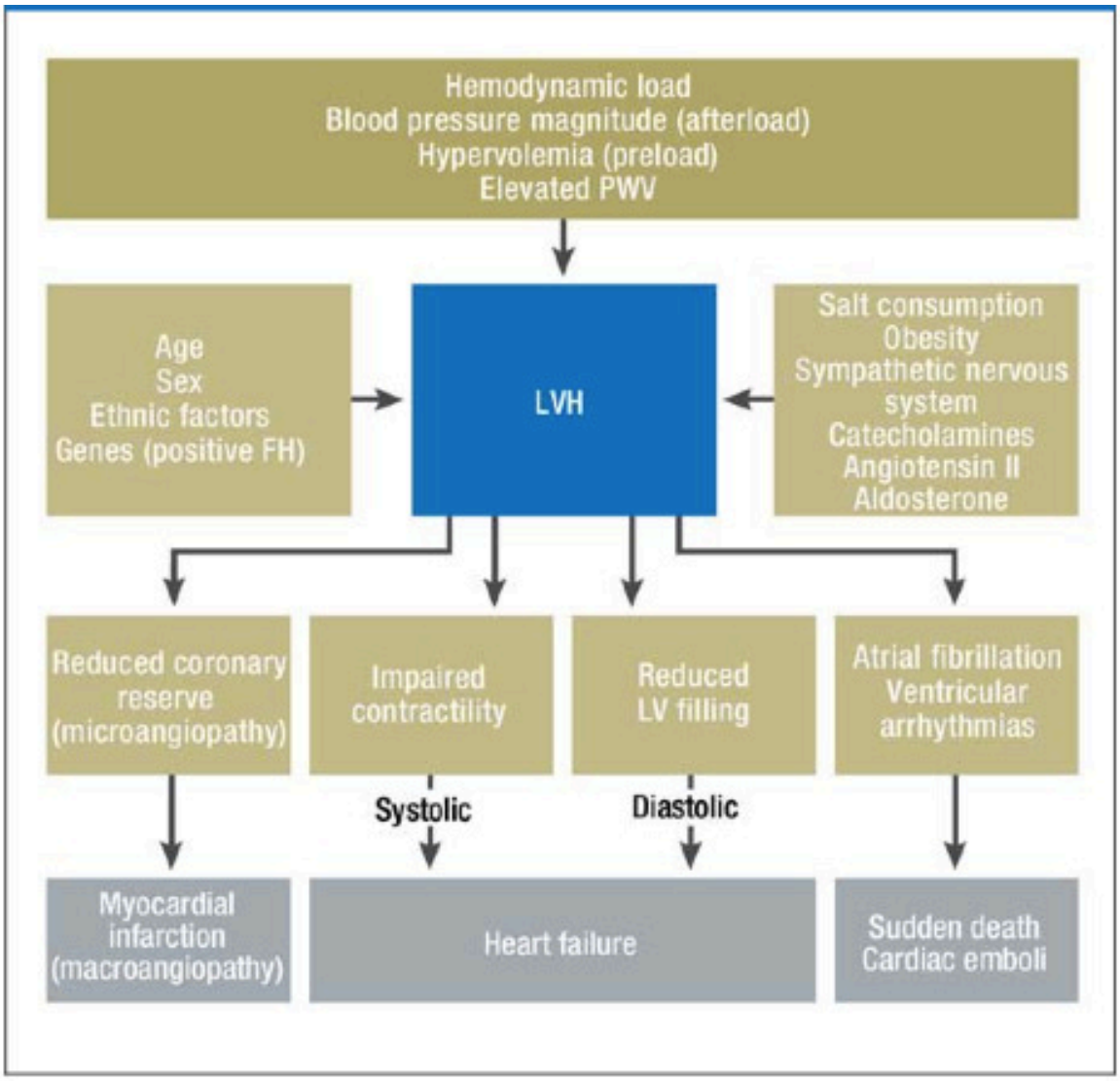
Table 1.2. End organ damage in hypertension

Organ	End organ damage
Heart	• Left ventricular hypertrophy • Atrial fibrillation/arrhythmias • Coronary artery disease/microangiopathy • Congestive cardiac failure
Blood vessels	• Endothelial dysfunction • Remodelling of vessels • Generalised atherosclerosis • Aneurysm • Microangiopathy (retinopathy)
Brain	• Stroke • Lacunar infarction • Intra cerebral haemorrhage • Acute hypertensive encephalopathy
Kidney	• Microalbuminuria/proteinuria • Chronic kidney disease/renal failure

1.1.A2. Hypertensive heart disease

Hypertension causes structural and functional pathologies in the heart (32), amongst which LVH is of much importance, and plays a central role in inducing different pathologies and complications in the heart (Figure 1.3) (31). LVH causes impaired left ventricular relaxation and thereby it causes delayed diastolic filling. In the late stage, the compliance of the left ventricle is reduced, with ensuing diastolic heart failure. Electrocardiography (ECG) will provide reliable clues regarding the diagnosis of LVH, and the commonly used criteria is Sokolow-Lyon index (33), which is shown in the Figure1.4. However, acquisition of an echocardiogram serves as the diagnostic test for hypertensive heart disease, which assists with measurements of the dimensions of chambers, and also function of the heart. Left ventricular masses greater than 259 grams in men, and 166 grams in women, are considered abnormal (23). LVH is considered to be present if the relative wall thickness was greater than 0.43 and/or LV mass is increased (23).

Figure.1.3. hypertensive heart disease – pathogenetic factors and clinical implications



Hypertensive heart disease: pathogenetic factors and clinical presentation. PWV, pulse wave velocity; FH, family history; LVH, left ventricular hypertrophy; LV, left ventricle

Legend: Figure reproduced from Schmieder RE(31)

LVH causes myocardial infarction, heart failure, arrhythmia, embolic phenomena and sudden death (31). However, a reduction in LV mass reduces the risk of cardiovascular events by more than 50% (34). Indeed, an LV mass change of more than 35 g between two different measurements is considered significant in view of variability between the echocardiographic measurements made by observers (31, 34). ACE inhibitors and angiotensin receptor blockers are the primary choices in such cases, and these effectively prevent the ventricular remodeling and also the further complications or pathologies induced by LVH (31). Beta blockers are used in the settings of tachyarrythmia in order to control heart rate.

1.1.A3. Hypertensive nephropathy

Chronic renal failure is the most common manifestation of hypertensive nephropathy, which often develops after 15 to 20 years (31). The easiest and earliest ways to detect hypertensive nephropathy are microalbuminuria and estimated glomerular filtration rate calculation (EGFR) (35). Leoncini et. al., demonstrated a significant change in the estimation of cardiovascular risk assessment based on the renal parameters microalbuminuria and EGFR for hypertensive end organ damage (35). In view of its molecular size, albumin can be traced to glomeruli through different layers such as endothelium, basement membrane and podocytes that are associated with increased permeability. However, this process is not restricted to renal vasculature but is also

observed in other vascular systems. Hence, albuminuria is a predictor for chronic renal insufficiency and cardiovascular events.

Microalbuminuria is a sensitive indicator for the early signs of nephropathy, and is also considered as a valuable tool in the diagnosis of coronary heart disease (36), which has been proved again in the HOPE study (37). Both the European Society of Cardiology and the European Society of Hypertension urged the clinical importance of screening for microalbuminuria in the 2007 hypertension guidelines (38). Also, these societies recommended the screening of microalbuminuria in the assessment of end organ damage and in all hypertensive patients because of its easy availability, detection and low price (38). In a study conducted amongst Singapore physicians, that the majority of doctors (about 88%) screen their patients for microalbuminuria (36).

Aggressive management to control hypertension and prevent the further progression of renal failure is mandatory in order to prevent renal failure and cardiovascular implications. In the LIFE study, hypertensive patients with LVH who were treated and showed a reduction in albuminuria had fewer cardiovascular complications (39). Concurrent findings have been noted in the RENAAL study, which also included diabetic patients(40). The recommended target blood pressure in hypertensive nephropathy is less than 130/80 mmHg; however, in the presence of proteinuria, it should be even lower (41). Numerous studies including large retrospective ones have confirmed the nephroprotective effects of ACE inhibitors/angiotensin receptor blockers and direct renin inhibitors (41, 42).

1.1.A4. Hypertensive retinopathy

Hypertensive retinopathy is considered as a significant risk, and prognostic indicators for systemic mortality and morbidity (29). Hypertensive retinopathy is graded into four categories according to the standard and old criteria 'Keith-Wagener-Barker' classification (illustrated in Table 1.3) (43).

Table.1.3. Keith-Wagener-Barker (KWB) classification of hypertensive retinopathy

Grade	Features
Grade I	Mild generalized retinal arteriolar narrowing
Grade II	Definite focal narrowing and arteriovenous (AV) nipping
Grade III	The above findings plus retinal haemorrhages, exudates and cotton wool spots
Grade IV	Severe grade III and papilloedema

The older criterion has been modified according to strategies and patient's approach towards the risk assessment of mortality and morbidities of cardiovascular diseases, and this is shown in Table 1.4(29). However, in this study, we have used the standard criteria, i.e. the Keith-Wagener-Barker classification (KWB classification) (44).

Table.1.4. Three Grades classification of Hypertensive Retinopathy and their Systemic associations(29).

Grades of retinopathy	Definition	Systemic associations
Mild	Grade I + Grade II of KWB classification	Weak associations with stroke and cardiovascular disease
Moderate	Grade III of KWB classification	Strong associations with renal failure, stroke and cardiovascular disease
Accelerated	Grade IV of KWB	Associated with increased mortality from any of systemic diseases

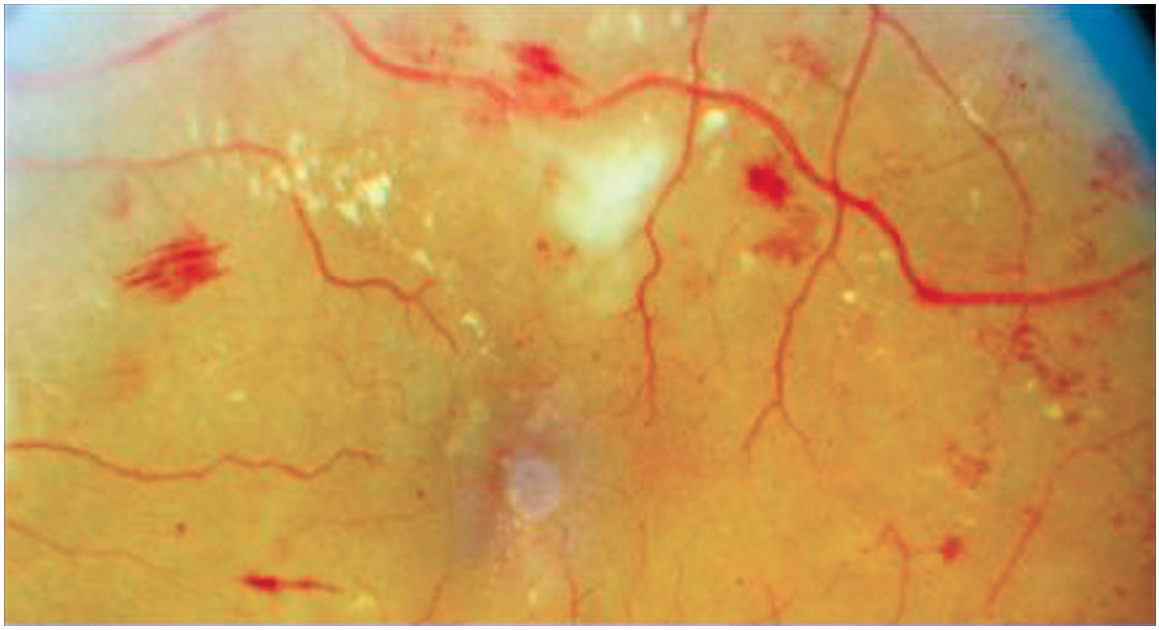
There are many population studies which have provided the data on the prevalence of hypertensive retinopathy with associated signs/grades (29, 45-52); The prevalence varied from 3 to 14% of the adult population (29). Table 1.5 provides the prevalence of hypertensive retinopathy with signs from different population-based studies (Figure reproduced from Wong etal.,(29). Figure 1.5 shows the typical exudates, hemorrhage and papilloedema(29).

Table.1.5. Prevalence of hypertensive retinopathy associated signs from different populated-based studies

Systemic associations	Haemorrhage	Microaneurysm	Cotton-wool spot	AV nicking	Focal arteriolar narrowing	General arteriolar narrowing
Current blood pressure	+++	+++	+++	+++	+++	+++
Past blood pressure				+++		+++
Carotid artery disease	+++	+++	+++			++
Clinical stroke	+++	+++	+++	++		+
Subclinical cerebral disease	+++	+++	+++	++		
Cognitive impairment	+++	+++	+++			
Coronary heart disease	+	+	+			++
Congestive heart failure	+++	+++	+++	+	+	+
Incident hypertension					++	++
Incident diabetes						++
Renal dysfunction	+++	+++	+++	+		
Cardiovascular mortality	+++	+++	+++			+
Inflammation				+		+
Metabolic syndrome	+	+	+	+	+	+

Legend: +++ : Strong association (relative risk/odds ratio is > 2), ++: Moderate association (relative risk/odds ratio is 1.5 to 2), +: Weaker association (relative risk/odds ratio < 2). The above data was tabulated by Wong etal.,(29) from different population based studies and the table is adapted from Wong etal., (29).

Figure.1.4. Fundoscopy revealing exudates, hemorrhage and papilloedema



Legend: The figure copied from Porta etal., (53)

1.1.A5. Rationale for the study

Medical societies dedicated to hypertension have focused not only on blood pressure for risk stratification, but also on other factors such as cardiovascular risk factors and the detection of EOD (24). Patients with grade I hypertension can be associated a mild or significant risk, depending on what additional EOD is present, and further co-morbidities such as diabetes, dyslipidemia, etc. In our system, most of the patients visit clinicians only when the symptoms are distressing, a phenomenon which is unlikely in the case of uncomplicated hypertension. Also, most physicians do not routinely check blood pressure in their patients regardless of the purpose of the clinic visit. Many young adult patients admitted to hospitals with one or other form of end organ damage made clear the essential requirements for this study. To the best of our knowledge, there are no published reports on covert EOD in newly-detected essential rural hypertensives from the Southern Indian region.

1.1.B. COMMON BUT IGNORED CAUSES FOR HYPERTENSION IN INDIA

Snake bite envenomation is a common problem in India in view of its vast rural areas. Hypertension, including malignant and urgent cases, are notable in those which require urgent intravenous anti-hypertensive medication in order to control blood pressure to avoid further complications. However, such pathogenesis is not commonly considered by physicians in such clinical settings.

Thyroid disorders are common in India. Indeed, hypertension is predominant amongst Asian populations. Hypertension in thyroid disorders is known, but is also less commonly considered in all thyroid disorder patients, nor to check for thyroid status in hypertensive cases, at least for resistant/malignant hypertension or hypertension with EOD, or patients with clinical signs or symptoms indicating thyroid dysfunction. Hence, we have included these studies in our research. Additionally, hypertensive patients with one or other forms of end organ damage on the background of thyroid dysfunction, and even with maximal anti-hypertensive therapy, blood pressure will not be adequately controlled unless the associated thyroid dysfunction is treated adequately. We have encountered few such patients while we were performing our evaluation of end organ damage in newly-detected hypertensives (however, they were excluded from the study in view of the exclusion criteria). These observations rendered our further study to investigate links between thyroid disorders and hypertension essential.

1.1.C. Hypertension in snake bite

Snake envenomation is a common medical emergency in India with an estimated mortality rate of 35,000-50,000 people per annum (54). Indeed, elapid snake envenomation has been recorded as a frequent occurrence in India, amongst which common (or 'Indian') krait species (Bungarus caeruleus) is also included. The classic symptoms observed in krait bite (which is often described as painless) are early morning symptoms such as abdominal pain or cramps (55), together with progressive muscular paralysis which often commences with ptosis. In this work, I present three cases of elapid envenomation with severe hypertension

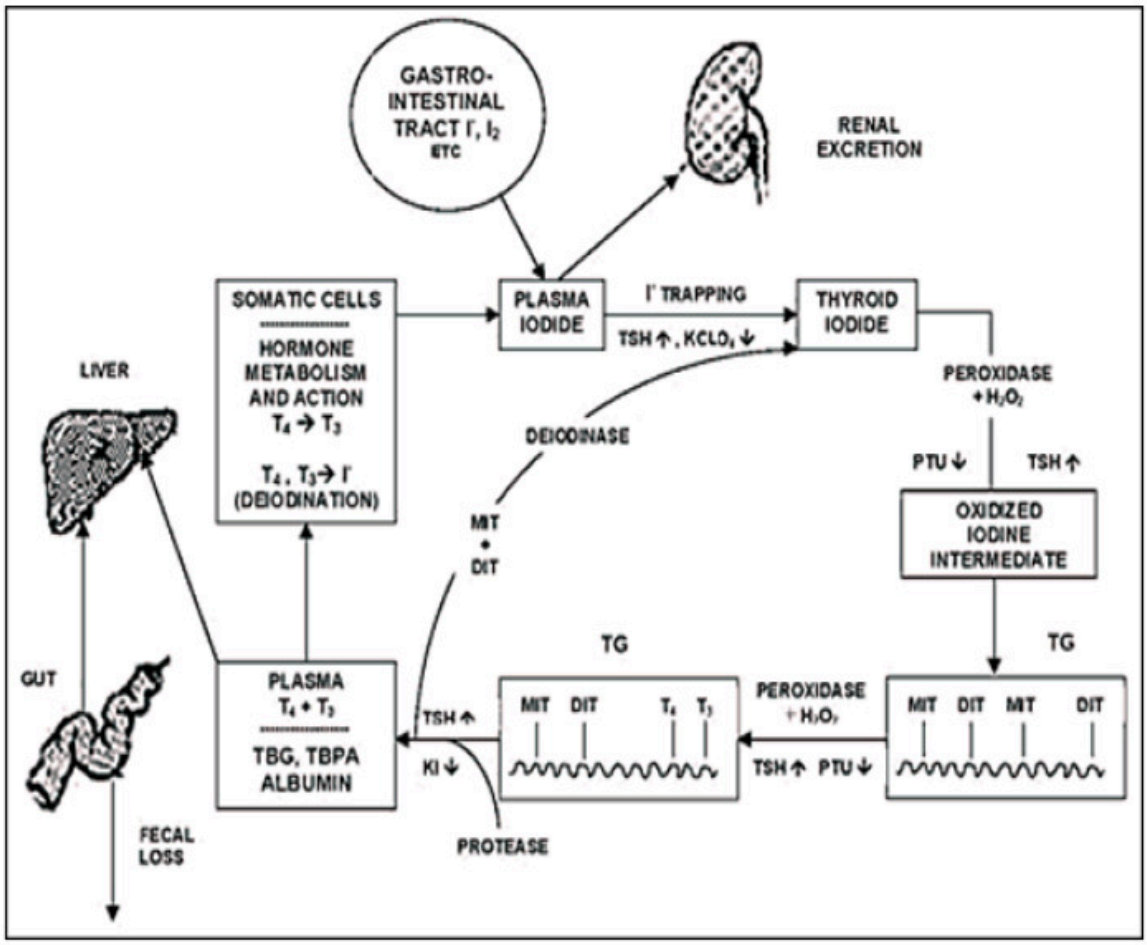
requiring intravenous anti-hypertensives. Interestingly, snake (krait) bite was unknown to all three individuals, but was brought to our attention after an elaborate history and the performance of a detailed physical examination. These cases are presented in order to create an awareness of such issues amongst those practicing under resource-limited environments in which snake bites are prevalent and frequently-encountered.

1.1.D. Hypertension in thyroid disorders

1.1.D1. Thyroid hormone metabolism

Thyroid hormones such as triiodothyronine (T3) and tetraiodothyronine (T4) are produced in the thyroid gland in a ratio of 1:7. The synthesis of thyroid hormones is via an enzymatic process which involves thyroid gland, pituitary gland, liver, kidney and skeletal muscle, and secretion is primarily regulated by the thyroid stimulating hormone (TSH)(56, 57). A schematic representation of thyroid hormone synthesis and secretion is provided in Figure 1.6 (57).

Figure 1.5. Thyroid hormone synthesis



Legend: Within the iodide cycle, ingested iodide is trapped in the thyroid, oxidised, and bound to tyrosine to form iodotyrosines in thyroglobulin (TG); coupling of iodotyrosyl residues forms T4 and T3. The hormones secreted by the gland is transported in serum (some T4 is deiodinated to T3). The hormone exerts its metabolic effect on the cell and is ultimately deiodinated; the iodide is then reused or excreted in the kidney. A second cycle goes on inside the thyroid gland, with deiodination of iodotyrosines generating iodide, some of which is reused without leaving the thyroid (57). The Figure 1.6 is reproduced from Miot etal., (57).

Thyroid hormones exert a range of actions on physiological systems of the body, including cardiovascular physiology. Thyroid dysfunction is associated with increased mortality

from, or a high prevalence of, cardiovascular diseases (58); deviations from euthyroid status affect normal physiology. Other than the well known effect of atherosclerosis in hypothyroidism, and also the risk of atrial fibrillation in hyperthyroidism, thyroid hormones exert a major effect on the heart and blood vessels (59). Cardiac output is maintained by peripheral vasoconstriction, arteriolar dilatation, blood volume and venous capacitance in response to the metabolic needs of tissue (59). Venous return is determined by blood volume and venous capacitance. Arteriolar dilatation decreases peripheral vascular resistance which increases afterload and cardiac output. A flow law chart which includes hemodynamic parameters, and each parameter which is influenced by thyroid hormone, is depicted in the figure 1.7 (59). In addition, thyroid hormones influence the autonomic nervous system, renin angiotensin aldosterone system (RAAS), renal function and vasoreactivity (59).

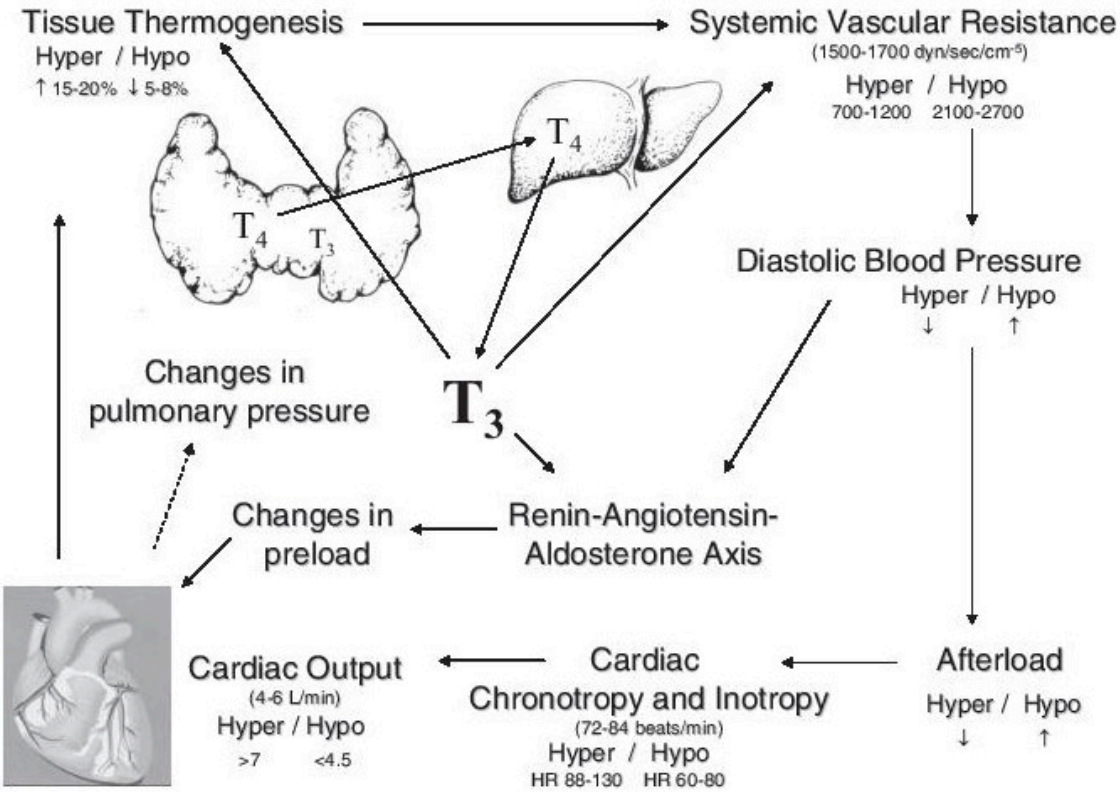
1.1.D2. Effect on thyroid hormones on Cardiovascular Physiology

Triiodothyronine (T3) is the major thyroid hormone which acts on the heart, and the effect of T3 in cardiac physiology is noted in Table 1.6 and Figure 1.8 (59, 60). Furthermore, Table 1.7 depicts changes in the cardiovascular function in thyroid disorders (60).

Table 1.6. Action of T3 on the heart (59, 60).

ACTION OF T3 ON HEART
Increases the speed and force of systolic contraction
Increases the speed of diastolic relaxation
Decreases vascular resistance
Increases coronary vascular tone
Increases coronary arteriolar angiogenesis

Figure 1.6. Thyroid hormone on cardiovascular hemodynamics



Legend: The figure is reproduced from Klein et. al.(61). T3 and T4 – Thyroid hormones, ↑- increase, ↓- decrease, hyper – hyperthyroidism, hypo – hypothyroidism, HR – heart rate

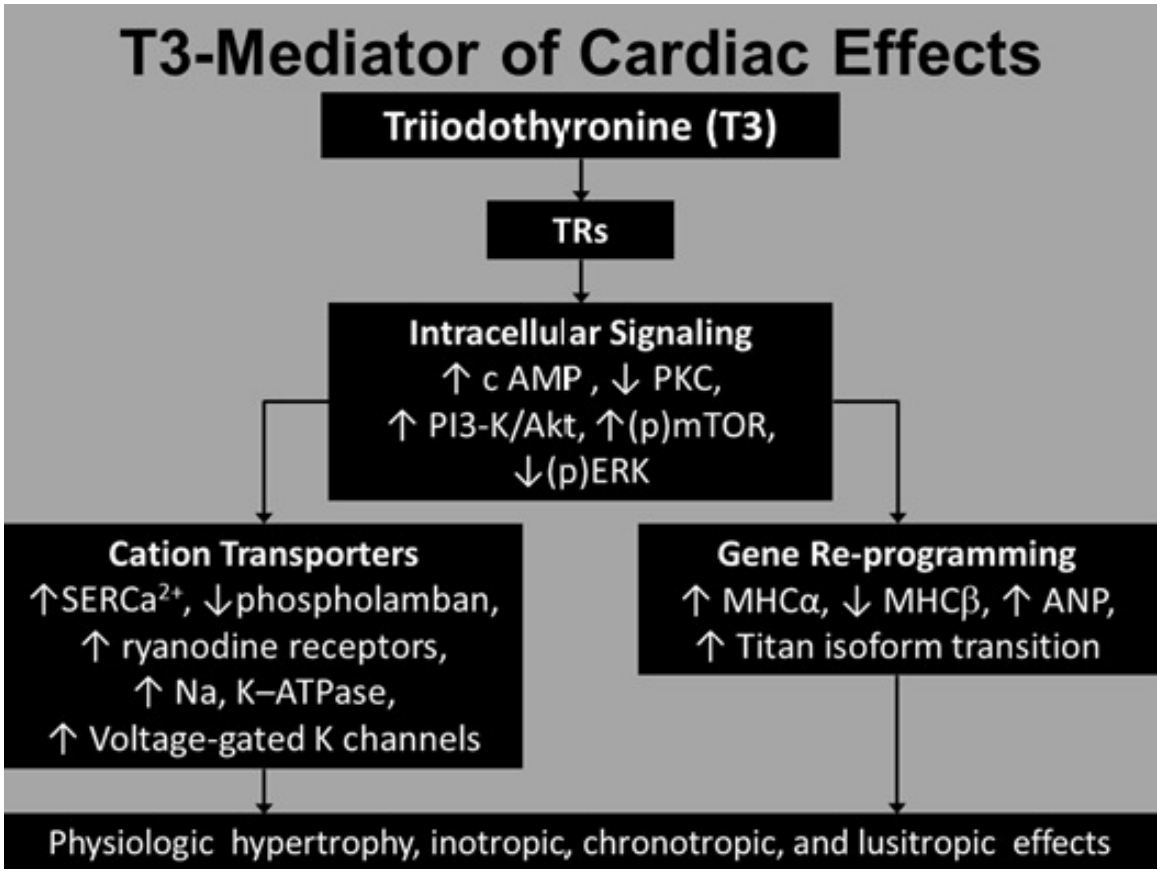
Table 1.7. Changes in Cardiovascular Function in Thyroid Disorders (60)

Parameters	Hyperthyroidism	Hypothyroidism
Heart rate	Increased	Decreased
Ejection fraction	Increased	Decreased
Cardiac output	Increased	Decreased
Blood volume	Increased	Decreased
Iso volumetric relaxation time	Decreased	Increased
Systemic vascular resistance	Decreased	Increased

Thyroid hormone action is generally mediated through the thyroid hormone receptors (TR), TR α (alpha) and TR β (beta)(59). The predominant receptor in the heart is TR α and T3 binds to TR α in cardiac myocytes(59, 60, 62-64), which in turn promotes the number of processes including protein (titan) transition through phosphorylation or activation of phosphoinositol 3-kinase (PI3-K), protein kinase B and the mammalian target of rapamycin (MTOR)(65-68). These are modulated by decreases in protein kinase C, and corresponding increases in atrial natriuretic peptide (ANP)(67, 68). Moreover, these changes induce alterations in gene expression and thus initiates cardiac hypertrophy. Alterations in gene expression includes a positive effect exerted on the transcription of the myosin heavy chain

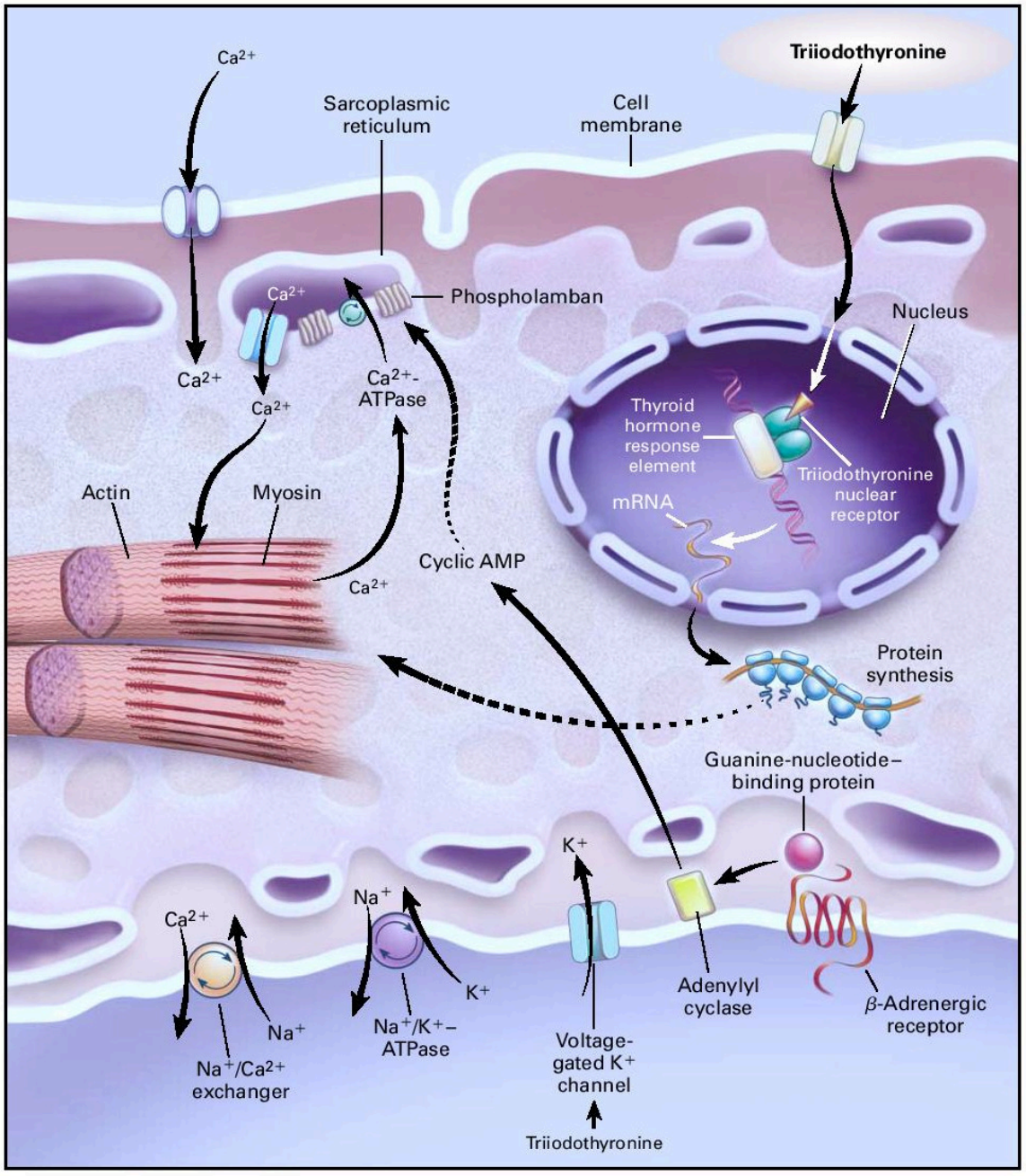
(MHC) α gene, and a negative effect on the MHC β gene(59, 60, 62-64). Thyroid hormones increase ATP (adenosine triphosphate) and gene expression of sarcoplasmic reticulum calcium ions (SRCa), together with a decreased expression of the MHC β gene. Overall, thyroid hormone inhibits SRCa through activation of SRCa ATPase and ryanodine channel, and an inhibition of phosphorylation of phospholamban, a substance present in the SRCa pump for activation (69-71). In view of this, diastolic function of the heart is affected due to poor contractility from low calcium ion in cardiac myocytes (59). T3 also promotes β1 adrenergic receptors and inhibits TR α receptors, which in turn mediates the inotrophic and chronotrophic effects of the heart (60). A summary of T3 action on the heart through various pathways is depicted in Figures 1.9 (59) and 1.10(60).

Figure 1.7. Thyroid hormone effects on the heart



Legend: Figure reproduced from Grais etal.(59). T3 = triiodothyronine; TR = thyroid hormone receptors; cAMP = cyclic AMP, PKC = protein kinase C; PI3-K = phosphoinositol 3-kinase; Akt = protein kinase B; (p) mTOR = phosphorylation of mammalian target of rapamycin; (p)ERK = phosphorylation of extracellular-signal-regulated kinases; SERCa2+= sarcoplasmic reticulum Ca2+; Na = sodium; K-ATPase = potassium adenosine triphosphatase; MHCα =myosin heavy chain alpha; MHCβ = myosin heavy chain alpha beta; ANP = atrial natriuretic peptide

Figure 1.8. Site of action of T3 in cardiac myocytes



Legend: (Figure reproduced from Klein etal. (60). Ca – calcium, K – potassium, Na – sodium, AMP – adenosine monophosphate, ATP – adenosine triphosphate

1.1.D3. Action of Thyroid hormones on blood vessels

Thyroid hormones reduce the vascular tone and remodel the vessels. Various actions and mechanisms through which the thyroid hormone T3 influences the blood vessels are tabulated in Table1.8.

Table 1.8. Actions and mechanisms of thyroid hormone (T3) on the blood vessels

Action	Mechanism through which
Relaxation of vascular smooth muscle(60)	(i) reduces expression of angiotensin II type 1 receptor(72) (ii) reduces the calcium ion production and sensitivity(72) (iii) reduces contractile response to angiotensin II(72) (iv) stimulates nitric oxide production via activation of protein kinase B and phosphoinositol 3-kinase(73) (v) decreases myosin light chain phosphorylation and phenylephrine(73)
Promotes angiogenesis	Remodelling of vessels and endothelial dysfunction (74)
Increases the density of small arterioles	Remodelling of vessels(74)

Whilst atrial fibrillation and atherosclerosis are commonly reported in thyroid disorders, thyroid dysfunction causes multiple pathologies in the heart as listed in Table 1.9.

Table 1.9. Thyroid dysfunction and cardiovascular pathology

Organ/system	Pathology (pathogenesis)
Heart	Systolic and diastolic heart failure (downregulation of thyroid hormone receptor) (60, 74)
	Atherosclerosis (through multiple mechanisms such as effects on blood vessels, dyslipidemia, endothelial dysfunction and others as noted above)(59, 60)
	Tachy- and brady-arrhythmia, most common is atrial fibrillation (through receptor and hormonal pathways)(59, 60)
	Valvular disease (through chamber dimension changes and high flow)(60)
	Pericarditis, pericardial effusion (through inflammatory process and volume retention (59, 60, 75))
Vascular system	Systolic and diastolic hypertension (mechanisms described in Table 1.9)

1.1.D4. Hyperthyroidism

Biochemical definitions of hyperthyroidism include low plasma or serum TSH and high T4 or T3 levels, or both. Etiologies include Graves disease, thyroid nodules, iatrogenic overdosage and autoimmune thyroiditis. The common symptoms include thin body weight in spite of excessive appetite, moist skin, feelings of warmth, intolerance to heat, loss of body hair, diarrhoea, palpitations, headache, in addition to nail changes. Early treatment with anti-thyroid medications is mandatory in order to prevent complications. Thyroid storm or crisis is a life-threatening complication of hyperthyroidism, usually precipitated by acute illness, stress or infection. Patients involved require urgent treatments with antithyroid medication including beta blockers (which converts the peripheral conversion of T4 to T3), and other supportive treatments. Complications of hyperthyroidism are listed in the Table 1.10(59, 60).

Table 1.10. Complications of hyperthyroidism

Systolic hypertension
Increased LV mass
Poor exercise tolerance
Angina
Tachyarrhythmia, the common one is atrial fibrillation
Heart failure (high output failure)
Heart valvular disease

1.1.D5. Sub-clinical hyperthyroidism (SCH)

Patients presenting with low blood plasma/serum TSH but normal T3 and T4 levels are considered as having sub-clinical hyperthyroidism. Previous studies, including the Rotterdam study(76) concluded that SCH carries a similar risk and complications as hyperthyroidism, and hence such patients require the regular monitoring of overt thyroid disease and associated complications(76-78). The need for treatment for SCH depends on the level of TSH, the aetiology of SCH, and associated co-morbidities(59).

1.1.D6. Hypothyroidism

Hypothyroidism is defined by low levels of T3 and T4 with raised TSH (through inhibition of negative feedback hormone). The clinical manifestations include fatigue, change in voice, constipation, plus intolerance to cold and skin changes. Treatments for hypothyroidism include replacement with thyroid hormones; however, a slow and cautious approach is mandatory. Complications of hypothyroidism are listed in Table 1.11 (59, 60).

Table 1.11. Complications of hypothyroidism

Hypertension (diastolic and systolic)
Brady arrhythmia, the common one is sinus bradycardia
Heart failure (systolic and diastolic)
Dyslipidemia
Metabolic syndrome
Atherosclerosis including coronary artery disease, angina
Endocardial fibrosis
Myxomatous valuvular changes
Pericarditis and pericardial effusion

1.1.D7. Sub-clinical hypothyroidism (SCHO)

SCHO is defined as high blood plasma/serum TSH, coupled with normal levels of T3 and T4. Like SCH, SCHO carries the risk and complications similar to hypothyroidism. However, the treatment depends on the level of TSH, aetiology and co-existing illnesses (59, 60).

1.1.D8. Rationale of the study

Although the effect of deviations from euthyroid status on blood pressure (BP) is more marked (79, 80), the relationship between thyroid disorders and BP is not well recognised (81). Moreover, to date a series of contradictory relationships have been noted. Indeed, a

linear relationship between serum TSH levels and BP (both systolic and diastolic) was observed by Asvold et. al. (82, 83). However, no such associations were observed in two further studies (84, 85). Physiologically, BP is maintained via cardiac output (CO) and systemic vascular resistance (SVR), and hence BP is calculated using the CO x SVR formula. As discussed above, through multiple mechanisms thyroid hormones maintain heart rate, cardiac contractility and blood volume, and hence exert an important influence on BP. In addition, thyroid hormones regulate BP through the renin-angiotensin-aldosterone system (RAAS), in which hyper and hypothyroidism induce opposite effects (81). Moreover, thyroid disease can cause endothelial dysfunction through reduced fibrinolytic activity and nitric oxide (NO) synthesis (58). At the molecular level, thyroid hormones play an important role in the gene expression of cardiac myocytes (61). Furthermore, hypothyroidism has been associated with one or other metabolic syndrome components such as hyperlipidemia, diabetes and obesity (86).

In this investigation, I have explored inter-relationships between thyroid dysfunctional status, together with their associated biomarkers and a range of BP components [specifically systolic BP (SBP), diastolic BP (DBP), Mean Arterial Pressure (MAP), and uniquely SBP:DBP ratio] monitored in a very large number of healthy control, hypothyroid and hyperthyroid patients.

1.1.E. Knowledge, attitude, behaviour and practice (KABP) among the physicians towards blood pressure management

In countries with limited resources, the diagnosis of hypertension (HTN) is made by using mercury sphygmomanometers in clinical practice. Many technical errors might occur related to the equipment used in practice, and this could influence blood pressure readings. Inaccurate and unreliable equipment can lead to erroneous diagnosis with serious consequences for the patient (87). The American Heart Association (AHA) (88) recognises three sources of error in the measurement of BP: observer bias, faulty equipment and failure to standardise the techniques of measurement. International studies confirm that teaching, training and knowledge regarding blood pressure measurements and management for health care professionals are sub-optimal (89) (90) (91). Also, these gaps in training are continuing in medical education, and amongst interns and practitioners (90), (92). Hence, we have performed a questionnaire study focused on hypertension amongst physicians who manage this critical condition.

1.1.F. Awareness of hypertension amongst the general public

As discussed above, cardiovascular disease is the leading cause for mortality worldwide (93-96), and hypertension is a leading independent risk factor for cardio-cerebro vascular disease (96). In previously published studies concerning hypertension with complications, many of the patients were not even aware of this condition, and many subjects were unaware of the complications of it (97). In a PatenT study conducted throughout the Turkish population with 1,804 hypertensive patients, 59.3% of the subjects were not even

aware of hypertension, and only 8.1% of the subjects had adequate control (97, 98). Hypertension awareness amongst the Indian population was significantly lower than the awareness for diabetes (12). There was also a significant difference between awareness amongst rural and urban populations (12, 98). A further study, which compared the awareness of hypertension amongst Indians living in Singapore and rural India, has demonstrated a significant awareness within this urban population (99). In a recent study from India, amongst 6,106 subjects, awareness regarding hypertension was observed in only 55.3% of those surveyed, and the number of hypertensive subjects with an adequate control of blood pressure was sub-optimal (16). This is the current status not only in India, but also elsewhere (100). Lack of awareness of hypertension leads to sub-optimal control of blood pressure, a process which leads to reversible or irreversible end organ damage (16, 100, 101). Hence, there is urgent requirement to study the awareness of hypertension amongst the Indian population.

1.2. Objectives of the study

Considering the increasing prevalence of hypertension and its associated complications amongst Indians and also worldwide, this study was focused on determining the prevalence of EOD sequel in newly detected essential hypertensives without any other associated conditions. Also, the pattern of these EODs and their inter-relationships with age, gender and hypertension have been analysed. Whilst recruiting the patients for this study, I came across many with an inadequate control of blood pressure. Amongst them, more than 40% of patients have secondary causes of hypertension, and the most common cause encountered was thyroid disorders. Moreover, such patients were resistant to anti-hypertensive drugs without their dysthyroid status being corrected. However, these patients were excluded from this study (status of EOD in newly detected essential hypertensives) in view of co-morbid illness as one of the study's exclusion criteria.

Common but simply ignored causes of hypertension in India include thyroid disorders and snake envenomation. In this study, I have presented cases of elapid envenomation experiencing severe hypertension. Furthermore, the primary objectives to explore inter-relationships between thyroid dysfunctional status, together with their associated biomarkers and also a range of BP components [specifically systolic BP (SBP), diastolic BP (DBP), Mean Arterial Pressure (MAP), and uniquely SBP:DBP ratio] in a very large number of healthy control (euthyroid), hypothyroid and hyperthyroid patients have also been completed.

For any diseases, physicians' knowledge and patient awareness about the particular disease are mandatory measures for the disease identification, treatment, control and prevention. There are a very large number of reports available (published elsewhere) which have revealed that such measures for patients with hypertension are lacking. Additionally, press reports and lay media pronounce more information concerning diabetes rather than hypertension. Hence, in this study I have included a measure to study the knowledge, attitude, behavior and practice of blood pressure management amongst physicians in India, and also to explore the awareness of hypertension amongst the Indian general public.

CHAPTER 2. Status of end organ damage in newly detected hypertensives

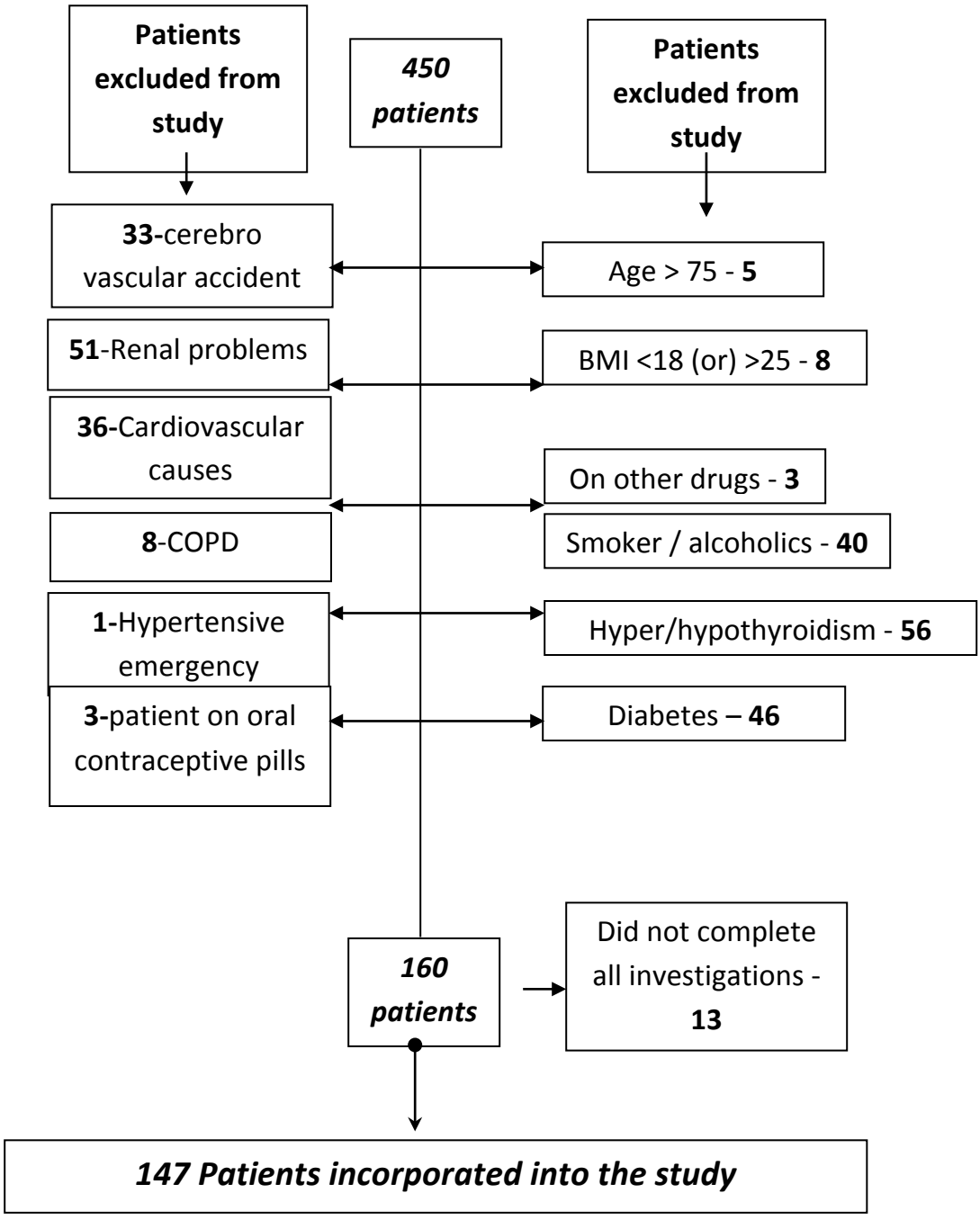
2.1.Methodology

This study was performed at the tertiary care hospital, India after the receipt of informed consent from the recruited patients and institutional ethical clearance according to Helsinki Declaration guidelines.

Study population

A total of one hundred and forty seven (n = 147) patients with newly-diagnosed essential hypertension, attending the outpatient clinic, were included for this present study based on a set of inclusion and exclusion criteria out of 450 patients consecutively seen, (patients with co-morbid illnesses were excluded from the study). The exclusion of other patients is given in the patient flow chart, (Figure 2.1). All cases were subjected to a complete history and physical examination with routine blood investigations. In addition, fundus examinations, 24-hour urine samples, electrocardiograms (EKG/ECG) and echocardiograms (Echo) were completed for all of the patients involved.

Figure 2.1: Patient flow-chart



Essential Hypertension

The blood pressure was taken as the mean of 3 readings in a relaxed and comfortable arm mode, and was based on standardised measures. All the cases in our study did not have any secondary causes of hypertension. Hypertension was defined and staged according to the seventh report of the Joint National Committee (JNC VII report) (102).

Retinopathy

Retinal examinations were performed in a dark room after instilling mydriatic agents, and were evaluated by a skilled ophthalmologist who had no prior information regarding the patients. Retinal lesions were assessed according to the Keith-Wagener-Barker classification (44).

Microalbuminuria

Urinary albumin levels were measured in 24-hr. urine collections after excluding urinary tract infection as an interferent. Microalbuminuria was defined as urinary excretion of 30-300 mg of protein per day (103). In order to limit false-positive results, all patients were advised to avoid heavy physical exercise during the 24-hour collection period.

Electrocardiogram(EKG)

EKGs was taken in all patients in order to assess the evidence of LVH. The Sokolow-Lyon index criterion was used to diagnose LVH by EKG (33).

Echocardiogram

2-D and M-mode Echo was performed on each patient in supine position to assess the LV function and morphology according to the American Society of Echocardiography Guidelines. LV masses greater than 259 grams in men and 166 grams in women was considered abnormal (23). LVH was considered to be present if the relative wall thickness was greater than 0.43 and/or LV mass is increased (23).

Diastolic dysfunction

Diastolic dysfunction was assessed using mitral E/A, deceleration time and iso-volumetric relaxation time (IVRT). The values of mitral E/A less than 1, deceleration times of greater than 240m/sec, and IVRT values greater than 90m/sec were taken as diastolic dysfunction (104).

Systolic dysfunction

An ejection fraction of 50-80 % was considered within normal limits. Values less than this were considered as systolic dysfunction (105).

Statistical analysis

Baseline characteristics of study patients were expressed as means ± standard deviations. Student's t test was performed to determine the significance of mean differences observed between dependent variables, and ANOVA was used for those between independent variables. Moreover, the Chi-squared test was used to investigate the associations between

multiple variables, and associations between multiple variables such as systolic hypertension, diastolic hypertension, retinopathy microalbuminuria, LV mass, mean arterial pressure (MAP) and mitral E/A were explored using multiple logistic regression. A p value of ≤ 0.05 was considered as statistically significant. Statistical analysis was performed using the STATPAGES program (106).

2.2.Results

Demographic and clinical characteristics

Amongst the 147 selected cases, there were 79 males (M) and 68 females (F). Their mean and median ages were 55 ± (standard deviation (SD) = 9.90) and 54 years respectively; 24 patients were less than 45, 94 were between 45 and 64, and the remainder were more than or equivalent to 65 years of age. The distribution of systolic, diastolic and mean arterial pressures amongst them is depicted in Table 2.1. Within subject groups, 37 and 110 patients were categorized under JNC class I and II criteria, respectively. Amongst subject groups, 126 (86%) of patients (70 M and 56 F) had one or other EODs, an observation which was very nearly statistically significant ($p = 0.054$).

Table 2.1: Mean ± SD blood pressure values amongst subjects in the three age-group cohorts

	Age group (in years)					
	Male (n = 79)			Female (n = 68)		
BP	< 45	45-64	≥ 65	< 45	45-64	≥ 65
SBP	152±14	166±16	163±13	167±13	166±16	176±15
DBP	100±8	97±11	88±11	104±18	105±15	98±16
MAP	86±15	102±16	104±15	98±12	96±15	111±14

Abbreviations: SD = Standard deviation; BP = Blood pressure; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; MAP = Mean arterial pressure; n = Number of subjects.

Microalbuminuria

Out of 147 patients, 51 (35%) had microalbuminuria. With reference to age group, microalbuminuria was noted amongst 8 (4M & 4F), 32 (13M & 19F) and 11 (8M & 3F) cases in the age groups of less than 45, 45 - 64, and 65 and above years of age respectively. There was no association between microalbuminuria, and age or gender. Further analysis with Student's t-test revealed that there was no correlation of microalbuminuria with systolic and diastolic blood pressures, nor the mean arterial pressure.

Retinopathy

Amongst the subject groups, 102 (69%) had retinopathy and its association with hypertension was highly significant (p=0.01). The involvement of retinopathy amongst

subject groups, with special reference to age and gender, is shown in Table 2.2. However, there was no significant association between retinopathy and gender or the age groups less than 45, and 45-64 yrs. However, there was a correlation between old age (≥ 65 yrs) and retinopathy (as expected). None of the patients had grade IV retinopathy.

Table 2.2: Relationship of retinopathy to age and gender

Retinopathy Grade	Age Group (in years)					
	< 45 (n=24)		45-64 (n=94)		≥65 (n=29)	
	Male	Female	Male	Female	Male	Female
0	3	9	9	15	9	0
I	5	1	28	20	6	1
II & III	3	2	10	12	6	8
Total with HR	8	3	38	32	12	9
Total with HR	11		70		21	

Abbreviations: n = Number of Subjects; HR = Hypertensive retinopathy

Left Ventricular (LV) mass

Increased LV mass was noted amongst 100 (68%) cases, and the mean values were 264.85 (± 71.79) and 231.59 (± 74.86) grams amongst males and females, respectively. This difference was significant (p=0.007, t value=2.74) amongst males but was not found to be significantly age-dependent.

Diastolic dysfunction

Patients recruited to the study with diastolic dysfunction had only a grade I status (relaxation abnormality). The mean and the median mitral E/A values were 1.091 ± 0.513 and 0.91 respectively. Amongst the cases, diastolic dysfunction was observed in 53 males (67.1%) and 33 females (48.5%), and it was found to be independent of both age and gender.

Association of multiple factors

The distribution of cases according to gender with retinopathy and with or without microalbuminuria is shown in Table 2.3.

Table 2.3: Gender classification of patients with retinal Involvement with and without microalbuminuria

Microalbuminuria	Retinal involvement (n=102)					
	Grade 0		Grade I		Grade II & III	
	Male	Female	Male	Female	Male	Female
Absent	18	22	31	14	5	6
Present	3	2	8	8	14	16
Total with MA	5		16		30	

Abbreviations: n = number; MA = Microalbuminuria.

Statistical analysis with ANOVA revealed that there were significant differences between gender, retinopathy and microalbuminuria ($p = 0.0001$, ANOVA $p = 0.0002$). Also, retinopathy was higher in patients with microalbuminuria, greater LV mass ($p = 0.034$) and

diastolic dysfunction (p = 0.014). The distribution of LV mass and retinopathy with reference to gender is illustrated in Table 2.4.

Table 2.4: Retinopathy incidence according to grade, left ventricular mass and gender

Ret. Grade	Male (n=79)			Female (n=68)			t value	*p* value
	Number of Patients	Patients with Abnormal LV mass, n	Mean LV mass in grams	Number of Patients	Patients with Abnormal LV mass, n	Mean LV mass in grams		
0	21	8	220.198	24	11	181.92	2.17	0.037*
I	39	27	274.23	22	19	274.23	0.14	0.89 (ns)
II & III	19	16	294.95	22	19	240.41	2.64	0.013**

Abbreviations: n = Number of subjects; Ret. Grade = Retinopathy grade; Abnrl = Abnormal, LV mass = Left ventricular mass; *and ** = statistically significant at the 5% and 2% levels respectively; ns = not significant.

There was a significant association between increased LV mass and grade II and III retinopathy; however, this was not observed in grade I retinopathy. Furthermore, there was a correlation between stage II JNC and increased LV mass (p = 0.01), but not with stage I JNC (p = 0.63). The number of cases of left ventricular hypertrophy diagnosed by echocardiography was greater than those diagnosed by electrocardiogram, and the difference was statistically significant (p = 0.0003). We also found a strong association between LV mass and giddiness (p = 0015); however, there was no such association with other symptoms such as headache, chest discomfort and breathlessness. Statistical analysis using ANOVA found that diastolic dysfunction (mitral E/A) was significantly correlated with hypertensive retinopathy (p = 0.00005). A Chi-square test performed with IVRT and

deceleration time against retinal changes found highly significant p values of 0.0001 and 0.00025 respectively. A correlation matrix was computed from the major variables involved in the study and this is shown in Table 2.5. Microalbuminuria was found not to be dependent on blood pressure levels, but it was positively correlated with retinopathy, LVH and diastolic dysfunction. There was, however, a positive correlation between retinal changes and systolic blood pressure, but not with diastolic blood or mean arterial pressures. LV mass was associated with microalbuminuria and diastolic dysfunction, but not with blood pressure. LV mass had a strong positive relationship with diastolic dysfunction and microalbuminuria. However, none of the patients recruited to the study group had systolic dysfunction.

Table 2.5: Pearson correlation coefficients (r values) for relationships between the major Variables involved in the study

Correlation	Diastolic HTN	HR	MA	Diast. Dysfun.	LV mass	MAP
Systolic HTN	0.2892**	0.2284*	0.1143	0.0393	0.0222	0.8186**
Diastolic HTN		0.1810	0.1215	0.0304	0.0661	0.3130**
Retinopathy			0.3309**	0.2882**	0.3461**	0.1176
Micro albuminuria				0.2898**	0.2734**	0.0405
Diastolic dysfunction					0.5807**	0.0208
LV mass						0.0176

Abbreviations: HR = Hypertensive retinopathy; LV mass = Left ventricular mass; MA = Microalbuminuria; HTN = Hypertension; MAP = Mean arterial pressure; Diast. Dysfun. = Diastolic dysfunction; * and ** = Significance of correlation coefficient (r) value (2-tailed test), p = 0 .01 and, 0.001 respectively.

2.3. Discussion

WHO/International Society of Hypertension (ISH) guidelines have emphasised the concept that clinical decision making in hypertensive patients should not only include the measurement of blood pressure, but also rely on the monitoring systems that assess the risk of cardiovascular events (22). These measures include the presence or absence of concomitant risk factors, EOD and diabetes. In our study, microalbuminuria (35%), diastolic dysfunction (59%), increased left ventricle (LV) mass (68%) and retinopathy (69%) were particularly notable in 86% of patients (107, 108). The presence of EOD in

hypertension indicates not only a high risk status, but also an indication to immediately institute an intensive management system for hypertension. Since most of the essential hypertensives had one or other EOD (9, 24), it is suggested that the screening of EOD should be made essential, at least in those above the age of 40 years with a linked retinopathy. Indeed, our observation that LV mass had strong association with microalbuminuria, diastolic dysfunction, grade II and III retinopathy confirms this. (109).

Although ambulatory blood pressure monitoring (ABPM) in uncomplicated essential hypertension is of little value, except in some specific conditions, it provides further information regarding the pattern of blood pressure, and it is also more closely related to the provision of evidence for EOD. Indeed, at-home blood pressure monitors have better prognostic significance than clinical blood pressure recordings (110). However, the implementation of such measures in resource-limited settings is difficult in view of economical or policy demands. Also, the detection of EOD is influenced by many factors, including the accuracy of diagnostic tools and the availability of facilities and trained manpower. It has been recognized that the Echo monitoring system is more sensitive and specific than EKG measurements and chest X-ray evaluation for the detection of LVH (111), observations which were similar to those made here. Furthermore, the screening of microalbuminuria as an early marker of early renal disease represents an independent predictor of cardiovascular risk in the general population, in addition to hypertensives and diabetic patients (112, 113). The European Society of Hypertension concedes the importance of Echo measurements, fundoscopy and microalbuminuria in the search for EOD occurrence in all hypertensive patients (114). The results of our study provide

evidence that the screening for EOD increases the proportion of hypertensive patients who should be classified as having a 'high-risk' status for cardiovascular mortality and morbidity (115).

According to a recent survey, the overall prevalence of chronic kidney disease (CKD) is reported to be increasing, and a major proportion of these patients have early CKD in the form of microalbuminuria. The prevalence of CKD defined by azotemia was reported to be only 0.79% amongst Northern Indians; however, the prevalence of early/sub-clinical CKD in the form of microalbuminuria was not considered. Hence, our observations must alert physicians to seek evidence for early CKD in hypertension and then initiate preventive/treatment strategies. Patients with a high body mass index (BMI), adverse lipid profile, risk factors for stroke, and recent vascular insults had a higher incidence for the development of microalbuminuria (108, 116-118). However, age and gender was not found to play a role in the development of microalbuminuria (23). Significant associations between microalbuminuria, retinopathy and LVH have previously been shown in many studies (23, 118, 119). Moreover, microalbuminuria was found to be associated with coronary artery disease and in the HOPE study, microalbuminuria was selected to be of comparable value with respect to the diagnosis of coronary artery disease (119, 120). These observations provide much evidence that microalbuminuria serves as a marker of generalized endothelial damage, and The European Society of Hypertension in 2007 justified the assessment of microalbuminuria as a mandatory screening marker for all hypertensive patients (121).

Patients with one or other components of metabolic syndrome or diabetes often have hypertension, which in turn increases the risk of cardiovascular disease and nephropathy (122). Hence, it is ideal in clinical practice to perform microalbuminuria in all hypertensive patients. Common methods performed to screen for microalbuminuria are (i) albumin to creatinine ratio in random urine (ii) 24 hour urine creatinine clearance (iii) a urinary dipstick method, and (iv) measurement of albumin excretion rate in timed urine sample. In the United States, most physicians prefer a semi-quantitative urinary dipstick approach for screening.

The prevalence of LVH in our study of 68% was of a similar value to those reported in previous observations (123), and was greater in males, together with those with metabolic syndrome (MS) (124). However, another study from Southern India reported LVH in only 29% of their hypertensives (23). In this study, associations between age and LV mass were not found, which contrasts with the findings of Shirafkan *et. al.* (125). There is clearly a higher risk for cardiovascular events in hypertensives, coupled with higher risk factors for LVH with microalbuminuria. With regard to echocardiographic parameters, hypertensives with MS had an increased mean LV mass, wall thickness, left atrial size, longer deceleration time and LVH, an observation which concurs with earlier studies (124). However, we did not include MS as a component in this study. In MS, the trophic effect of insulin on myocardial tissues has been demonstrated *in vitro*, and this effect could be mediated through insulin-like growth factor receptors (126). However, conflicting results have been obtained regarding insulin status and LV mass in *in vivo* studies (126, 127). In the primary stages of hypertension, diastolic filling disorder can arise in view of a delayed

relaxation of LV, and subsequently, diastolic failure occurs as a consequence of poor LV compliance (128). These hypertensive patients with LVH had systolic and/or diastolic dysfunction, which concurs with previous observations (109). The pathogenesis of LVH in hypertension remains to be fully elucidated; several mechanisms for this process are hemodynamic stress, the duration and severity of hypertension (26, 129), and neurohumoral factors such as stimulation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, insulin, and further growth substances which enhance myocardial trophic responses (129). Aggressive treatment of LVH is mandatory to prevent serious complications arising from it. Table 2.6 provides the differential treatment considerations with regard to hypertensive heart disease and end organ damage (31).

Table 2.6. Treatment considerations for hypertension with end organ damage and hypertensive heart disease.

Subclinical end organ damage	
Left-ventricular hypertrophy	ACEI, ARB, CA
Elevated albuminuria	ACEI, ARB
Renal dysfunction	ACEI, ARB
Irreversible hypertensive end organ damage	
Prior stroke	Any antihypertensive
Prior myocardial infarction	BB, ACEI, ARB
Angina pectoris, CHD	BB, CA
Heart failure	Diuretics, BB, ACEI, ARB, MR antagonists
Left-ventricular dysfunction	ACEI, ARB
Atrial Fibrillation	
– Prevention, recurrence	ARB, ACEI
– Permanent	BB, non-dihydropyridine calcium antagonists
Tachyarrhythmia	BB
Chronic renal insufficieny, proteinuria	ACEI, ARB, loop diuretics
Peripheral arterial occlusive disease	CA

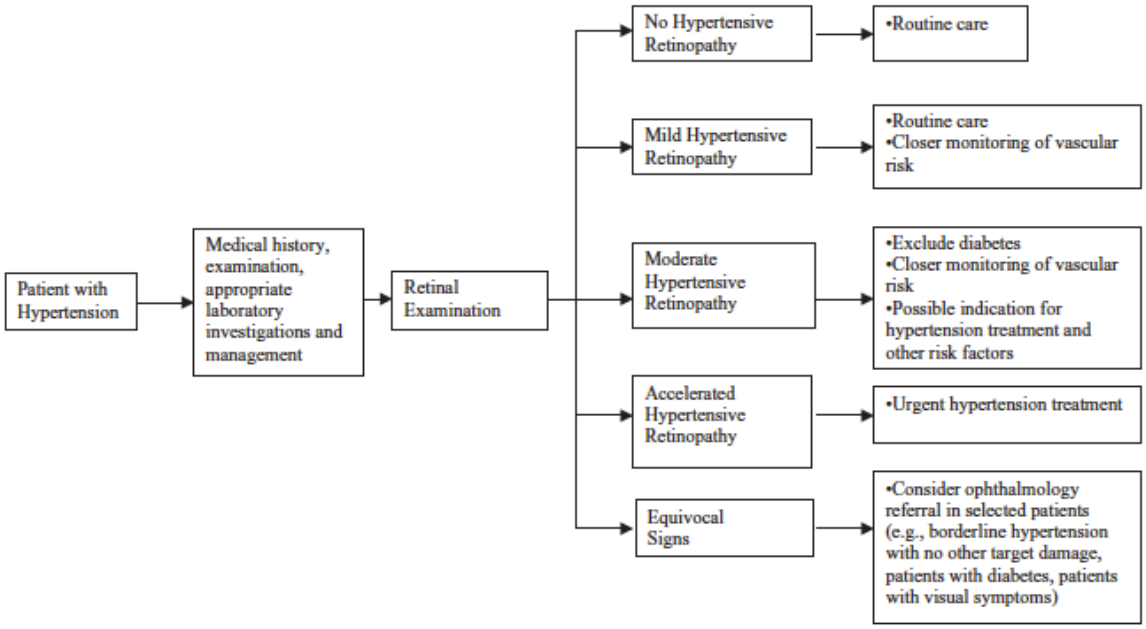
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker;
CA, calcium antagonist; BB, beta blocker;
MR-antagonist, mineralcorticoid antagonist;
CHD, coronary heart disease; MI, myocardial infarction

Legend: Table reproduced from Schmieder R. E. (31).

Our data suggest that hypertensive retinopathy could be considered as an early 'marker' of hypertensive EOD (108, 130). Indeed, increased blood pressure may damage the microvasculature and induce retinal arteriolar narrowing (131). Furthermore, the prevalence of hypertensive retinopathy is higher amongst patients with metabolic syndrome (124). It has been shown that there is a strong association between retinopathy and LVH (23, 118), whereas Gudmundsdottir et. al. (130) refuted this observation. In this study, there was a significant association between increased LV mass and grade II and III retinopathy, but not with grade I. It is therefore hypothesised that the duration and severity of excessive blood pressure may serve as major contributory factors for both these high risk conditions. Numerous previous studies have documented a strong association between hypertensive retinopathy and cerebrovascular diseases. Interestingly, the presence of hypertensive retinopathy may offer an additional predictive value for clinical stroke risk in patients with sub-clinical cerebral disease in imaging studies. In the ARIC study, participants with hypertensive retinopathy and with a MRI-defined white matter lesion had an 18 times greater risk for the development of clinical stroke than those without either one of these factors (132). Additionally, there is a high risk for incident coronary heart disease in patients with hypertensive retinopathy (133). Further, hypertensive retinopathy has been linked with many other systemic diseases such as heart failure, renal failure, inflammation, metabolic syndrome, cognitive impairment and cardiovascular mortality, which were all found to be independent of the grades of hypertensive retinopathy (29). Although fundoscopy has limitations for the detection of early hypertensive retinopathy (24, 134), it does not apply to grades III and IV. Therefore, fundoscopy remains an important tool

involved in hypertensive emergencies (24). Figure 2.2 depicts the evaluation and management of hypertensive retinopathy (29).

Figure 2.2. Evaluation and management of patients with hypertensive retinopathy.



Legend: Figure reproduced from Wong *et. al*. (29)

Retinal microcirculation provides a tool to assess the systemic microcirculation status. Coronary and cerebral microcirculation shares the similar anatomical and physiological properties with retinal microcirculation, and hence the pathology elsewhere will be reflected in the retinal microcirculation (135). In fact, retinal abnormalities may present in the early stage of hypertension which predicts the occurrence of future cardiovascular events (136, 137). Cuspidi *et. al.* observed early retinal changes in 78% in contrast to 22% for LVH and 14% for microalbuminuria amongst 800 hypertensive subjects studied (138,

139). Fundoscopy is the facile, safe and non-invasive test which provides us with much valuable information regarding the retinal vessels, and also aids the diagnosis of complications at an early stage (53).

There are some reports which include epistaxis as a form of evidence for EOD in hypertensives; however, this consideration is currently under debate (140). Indeed, the potential influence of blood pressure levels on epistaxis requires further investigation. In the general population, a blood pressure reduction to values less than 140/90 mmHg is recommended, and a target blood pressure of less than 130/80 mmHg is recommended for patients with evidence of organ damage or diabetes. The treatment of hypertension is based not only on blood pressure, but also on additional factors responsible for the pathogenesis of EOD.

2.3.1. Inflammatory and oxidative stress processes in end organ damage

Inflammatory processes are now being increasingly recognised in the pathogenesis of atherosclerosis (141, 142). Inflammation is one of the triggering process in various cardiovascular and cerebrovascular events, and thus inflammatory markers may be elevated in the hypertensive patients with end organ damage (141, 142). Association between C reactive protein (CRP) and future risk for heart attack, peripheral vascular disease, stroke and cardiovascular death amongst healthy populations have been published extensively (143-145).

Heamatocrit has been associated with hypertension and cardiovascular mortality (146). Moreover, whole blood viscosity may be implicated in the development of EOD in addition to further predictive factors for the development of hypertension as suggested above (130, 147). In animal models and hypertensive patients, endothelin receptor blockers reduce systemic blood pressure (148). Interestingly, clinical trials aimed at evaluating the efficacy of these drugs in the treatment of hypertension, and also in the management of EOD in hypertensive patients are underway. Relationships between the incidence of EOD and other mediators such as prorenin, renin and (pro)renin receptors have been previously demonstrated (149). Epoxyeicosatrienoic acid (EET) is synthesized from arachidonic acid, and exerts beneficial actions towards the cardiovascular system; however, it is converted to inactive components by a soluble epoxide hydrolase enzyme (EH). In animal models, inhibition of EH has been demonstrated to decrease blood pressure and inflammation, and also to protect organs against damage attributable to hypertension (150). Furthermore, an EET agonist has shown similar effects in animal model systems. and intriguingly these new and novel drugs have reached the point where they are now being evaluated in humans (150). It is suggested that 'oxidative stress' and inflammation may serve as denominators for the induction of end-organ damage in both diabetic and hypertensive populations. In addition, a role for α-7 nicotinic acetylcholine receptor (NAR) in inflammation has been identified. In hypertensive rats, a deficit in NAR leads to increased blood serum levels of pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-1β & 6), which were associated with morphological abnormalities in the heart, kidney and aorta (151). Treatment of hypertensive rats with an NAR agonist relieved EOD, and diminished the levels of pro-inflammatory cytokines. This study concluded that a defect in the cholinergic

anti-inflammatory pathway appears to contribute to pathogenesis of EOD, and this may provide a new therapeutic avenue for the modern era (151). Figure 2.3 demonstrates the schematic presentation of the mechanisms of end organ damage in diabetes and hypertension, in which hypertension exacerbates the process as noted (152).

2.4. Conclusions

Therefore, it is concluded that a very strong relationship exists between hypertension and EOD. The evidence for EOD was found to be greater than that expected in newly-diagnosed hypertensive patients. Hence, a tight control of blood pressure represents the first step in the treatment of essential hypertension, which not only retains control of the blood pressure, but also serves to prevent or delay the onset/progression of EOD. The presence of damage to one or more target organs signifies the requirement for a complete evaluation and immediate intensive therapy in the control of blood pressure and the treatment of such organ damage, which is likely to reduce the risk of cardiovascular mortality. An increased occurrence of EOD in hypertensives observed in this study indicates the unawareness amongst the general public, the attitude of physicians, or the laxity of the policy utilised for screening techniques. Blood pressure measurements should be regularly conducted in clinical practice regardless of the patient's age, sex and risk factors, and the specialty of the practice involved. Consensus guidelines for screening measures should be formulated and regularly practiced. Moreover, the physician's awareness of the clinical importance of screening measures in hypertensive patients may be strengthened through CME programs, which serve as surrogate markers for the prevention and/or treatment of EOD.

In view of covert end-organ damage, viz. microalbuminuria, retinopathy, higher left ventricular mass and left ventricular dysfunction observed amongst newly-detected, non-overweight, non-smoking, non-alcoholic and non-dyslipidemic essential hypertensives in

the rural areas in Southern India, there is therefore an urgent requirement to design and implement the "National Hypertension Detection and Control Program" by the Ministry of Health and Family Welfare (Government of India), with the help of professional medical associations and non-governmental organisations. Indeed, it is time to act (better late than never!), in order to prevent or minimise hypertension-induced complications.

2.5. Strengths and Limitations of Study

Rigid inclusion and exclusion criteria with the regular follow-up of patients served as the strengths. The limitations of the study were that it is a report from a single centre, and the population involved belonged to a low-income rural group.

CHAPTER 3. SEVERE HYPERTENSION IN ELAPID ENVENOMATION

In this Chapter, three cases of elapid envenomation with severe hypertension requiring intravenous anti-hypertensives is presented. Interestingly, snake (krait) bite was unknown to all three individuals, but was brought out after an elaborate history and the performance of a detailed physical examination. These cases are presented in order to create an awareness of such issues amongst those practicing under resource-limited environs wherein snake bites are prevalent.

3.1 Case - 1

A 26-year old male farmer was referred to the emergency room in the early morning from peripheral hospital for high blood pressure. He complained of giddiness, abdominal pain and vomiting. His past medical or family history was not contributory. He was a non-smoker, non-alcoholic, and not taking any form of medication. He had never been diagnosed to have hypertension, diabetes or kidney diseases, and was neither using traditional herbal medication, nor illicit drugs. He also denied febrile episodes, and any particular fear, anxiety or emotional distress. On admission, his supine brachial blood pressure (BP) was 240/180 mmHg with a strong peripheral pulse, and there was no significant difference in measurements between the arms. The physical examination, including fundus, revealed no abnormalities. Laboratory tests, including complete blood count, serum electrolytes (with an expected low potassium level), hepatic and renal function tests, coagulation profile, toxicology screen, urinary catecholamines, and renin/aldosterone, were unremarkable. An electrocardiogram showed normal sinus rhythm without any evidence of left ventricular hypertrophy. The urinalysis showed no proteinuria.

Chest radiograph, ultrasound of the abdomen, and a head-computed tomography scan were found to be non-contributory towards hypertension. Meanwhile, 90 min. after admission, he developed ptosis and external ophthalmoplegia, and complained of difficulty in breathing, swallowing and speaking. He became cyanotic and his level of sensorium started declining. He was electively intubated and mechanically-ventilated. Even with adequate sedation, there was a fluctuation in heart rate and the BP remained persistently high (range, 220–240 mm Hg systolic and 160–180 mm Hg diastolic). Though intravenous nitroglycerin (NTG) infusion was commenced in order to control hypertension, BP levels remained the same as those measured pre-infusion. The rapidly progressive ptosis, diplopia, dysphasia, dysarthria, dyspnoea and weakness raised a suspicion of neuroparalytic symptoms observable following snake-bite, which is common in rural Indian populations. Further careful examination of the patient's skin revealed a fang mark of snake-bite in the lateral aspect of the left leg with evidence of regional lymphadenopathy (he did not give a history of any possible snake-bite). On benefit of doubt, the injection of polyvalent anti-snake venom (ASV, 10 vials) was instigated. Throughout the next 6 hours, his neurological status and hypertension gradually improved, and then nitroglycerin infusion was tapered and terminated. He was extubated after 36 hr. of mechanical ventilation, and then discharged after 5 days of hospital stay (his BP during the hospital stay period was within normal limits). During the follow-up, he was found to be perfectly healthy with normal BP values.

3.2. Case - 2

A 24-year-old married woman was admitted to the Emergency Department (ED) of our hospital with a sudden episode of nausea, vomiting and abdominal pain, and became

acutely unwell whilst at work early in the morning. Her periods were normal and pregnancy test was negative. There was no past medical history, and she was not receiving any regular medications. On examination, she was of normal body weight, and afebrile with stable vitals. Her BP was 210/150 mmHg with no postural changes and without significant differences in these values between the arms. The physical examination and investigations (as outlined in case 1) were within normal limits. One hour after admission, the patient developed dysphagia and difficulty in breathing, following which she became delirious and experienced apnea. She was immediately put on ventilatory support. She had bilateral ptosis with reactive pupils. A thorough history of her family's dwellings and sleeping habits revealed the crucial evidence. Being farmers, they resided close to the fields and had frequently slept on the floor. Further careful examination of the patient's skin revealed a fang mark characteristic of snake-bite in the dorsum of her right foot, with evidence of regional lymphadenopathy. Based on clinical findings and corroborative evidences, 10 vials of polyvalent ASV in 100 ml of 0.9% saline was administered to her. During the following 6 hr., she displayed marked neurological improvement and her BP values diminished. She was weaned off the ventilator 36 hr. later and was discharged from the hospital on day 4. During the follow-up, she was perfectly healthy with normal BP levels.

3.3 Case - 3

A 35-year old male presented to the ED with abnormal sensations all over his body when he got up from sleep early in the morning. He also had nausea, abdominal pain and giddiness; he had no other significant past medical history. On examination, his BP was 200/140 mmHg with a normal general and systemic examination. The pertinent laboratory

parameters and imaging tests (detailed in case 1) revealed no abnormalities. He was kept under observation for further evaluation and NTG infusion was commenced. He subsequently developed acute paralysis with respiratory failure 2 hr. later on arrival at the hospital. He was intubated and then put on continuous mechanical ventilation. At this point, he had partial ptosis, dilated pupils, complete external ophthalmoplegia, and flaccid quadriparesis, with a flexor plantar response. A fang mark characteristic of snake-bite was seen in the lateral aspect of the right leg and he was started on a standard dose of inj. ASV. After 2 hr. of ASV infusion, he began to show spontaneous respiratory effort and required mechanical ventilation for a further 12 hr., although his BP became normal within 3 hr. of commencement of ASV. His neurological manifestations resolved over the next two days, and he was discharged after four days from his day of admission. Follow-up visits were uneventful.

3.4. Results

In all 3 cases, the snake was identified as a krait based on the classical history, clinical picture and increased incidences of krait bite in the local area. It is well known that kraits are active and agile at night, and during the rainy season they frequently seek refuge in dry places, such as those inside a house or dwelling place. Additionally, if humans are bitten by this snake during their sleep, they are seldom aware of it, since their experience of the bite generally resembles that from an ant or a mosquito, a phenomenon giving rise to a false level of reassurance to the victim.

3.5. Discussion

Elapid envenomation predominantly gives rise to neurotoxicity, a consequence of neuromuscular blockade, which manifests as paralysis of the bulbar, ocular, limb and respiratory muscles, leading to respiratory failure (153). The elapid venom contains both pre-synaptic and post-synaptic neurotoxins; however, krait venom exerts a predominant action in pre-synaptic neurons (153). Predominantly, pre-synaptic neurotoxins present in the venom of Bungarus species are highly potent and suppress the capacity of neuron endings to release biochemical transmitters. Transmitter release is primarily blocked subsequent to envenomation with such bangarotoxins (giving rise to a brief paralysis), a process followed by a period of substantial over-excitation (including cramps, spasms and tremors), which, in turn, leads to further paralysis.

Hypertension in our cases is probably ascribable to snake venom, since the secondary causes of hypertension were ruled out. Moreover, blood pressure levels normalised following ASV therapy, and the recoveries from neuromuscular paralysis observed indicate that krait venom might have contributed towards hypertensive episodes in such cases. Autonomic dysfunction following snake-bite may induce various symptoms such as abdominal pain, vomiting, sweating, and mild to moderate hypertension or hypotension, and cardiac arrhythmia. In a previous study, it was observed that more than 50% of the patients with krait bite had elevated blood pressure (154). However, severe hypertension subsequent to snake envenomation and requiring intravenous NTG is under-reported (155). The pathogenesis for autonomic dysfunction in snake bite is unclear. However, it may be attributable to the pre-synaptic alpha-2 adreno-receptor inhibition by elapid neurotoxin,

thereby blocking inhibition of the neutrally-mediated release of nor-epinephrine. Hence, this process gives rise to sympathetic over-activity and decreased parasympathetic stimulation (154, 156). A patient who was bitten by a Malayan krait experienced sweating, tachycardia, dilated pupil and hypertension arising from parasympathetic abnormalities (157).

In a case of a vipera berus bosniensis bite in Hungary, a high BP of 200/120 mmHg was recorded, with the victim responding promptly to the administration of an angiotensin-converting enzyme (ACE) inhibitor. Hence, the authors of this particular case report suggested that the venom of certain of the vipera population may contain cardiotoxin, which has potential to act at or via autonomic synapses (158); moreover, snake venom releases catecholamines which influence BP (159). Hypertension without neurotoxic symptoms was observed in patients with Western Russell's viper envenomation (160), and neurotoxic signs without hypertension was observed in an episode of the Eastern Russell's viper envenomation. It therefore appears that different toxins are responsible for cardiovascular and neurological symptoms (159). Further attributable causes for hypertension are pain, distress or hypoxia. However, severe hypertension in such cases is extremely rare. Additionally, the normalisation of blood pressure with improvements in

3.6. Conclusion

In conclusion, physicians should consider the possibility of severe hypertension in neurotoxic snake envenomation which may be ascribable to autonomic storm. Such patients may require intravenous NTG for the control of hypertension, together with other

conventional management protocols for snake bite. The drug of choice for the management of severe hypertension in such cases is NTG. Preferably, beta-blockers should be avoided in such situations where there is an excess of catecholamines, since these agents can precipitate severe alpha-agonist effects via the blockage of beta-receptor effects.

3.7. Strengths and limitations of the study

The fatal complication of snake envenomation, i.e. hypertension, is highlighted, as is the role of anti-hypertensive drugs to manage it. Limitations are the small number of subjects (patients) involved and non-confirmation of snake bite by immunoassay methods in view of technical limitations and the unavailability of facilities to perform such tests. Hence, more studies are warranted to establish the relationship between severe hypertension and snake envenomation.

CHAPTER 4. BLOOD PRESSURE COMPONENTS IN THYROID DISORDERS

4.1.Methodology

This study was performed at a tertiary care center in Southern India after the acquisition of approval from the Institutional research Ethics Committee, and also on receipt of informed consent from each participant recruited to the investigation. The ethical clearance approval was obtained from Ethical committee, Chennai Medical College Hospital & Research Centre, Trichy, India.

Subject criteria

Rigid inclusion and exclusion criteria were applied to recruit adult participants with thyroid dysfunctional status (established hypothyroid and hyperthyroid cases) and healthy control (euthyroid) subjects. Subjects with co-existing morbidities such as diabetes, post-thyroidectomy status, cardiovascular diseases, renal dysfunction and other illnesses were excluded from the study. Also, all the subjects recruited to this study were non-smokers (never smoked) and non-alcoholic, and all of them consumed normal salt intake. There were 71 hyperthyroid and 300 hypothyroid cases, and 300 control subjects.

Anthropometric (height and weight) and BP components were determined for all these participants. For the purpose of this study, the BP components considered are systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and SBP:DBP ratio. MAP values were computed using the [DBP + 1/3(pulse pressure)] formula, where pulse pressure represents the difference between the SBP and DBP values. Body mass index

(BMI) was calculated using the formula weight in kg/(height in meters)^2. A BMI value 23.0 and above was considered as overweight according to the WHO for Indians (161).

Thyroid function evaluation

Thyroid-stimulating hormone (TSH) and free thyroxine (T4) were estimated in all subjects by immunoradiometric assay (IRMA) using kits procured from Board of Radiation and Isotope Technology (BRIT), Mumbai, India. Normal reference population values of TSH and T4 are 0.17 - 4.05 IU/ml and 55 - 135 ng/ml respectively.

Statistical Analysis of Experimental Data Acquired

Univariate data analysis of SBP, DBP, SBP:DBP ratio, MAP, BMI, age, and blood serum TSH and T4 level indices [analysis of variance (ANOVA), analysis of covariance (ANCOVA) and χ^2 contingency table analysis] was performed using XLSTAT software. ANOVA and ANCOVA were conducted both with and without the inclusion of first-order interaction variance components, and also with a tolerance of 0.0001 and the computation of 95% confidence intervals (CIs) for the least squares means determined. In cases where there were heterogeneous intra-sample variances, comparisons of mean thyroid status values were performed using the Welch ANOVA method. *Post-hoc* analysis of the differences between the mean values of all group classifications was performed by Tukey's honestly significantly difference (HSD), Fisher's least significant difference (LSD), and the Bonferroni and Dunn-Sidak tests. Partial correlation coefficients [and their corresponding two-tailed significance (p) values] were computed between a MV dataset containing the

serum T4 and TSH biomarker concentrations (together with age and BMI values) and each of the BP components individually.

Multivariate Redundancy Analysis (RDA) was also performed with XLSTAT software, the model involving a minimum filter factor of 80%; permutations were performed 500, 1,000 or 2,000 times, and both response (BP) and explanatory (thyroid disease) variables were centered and reduced prior to analysis (a 1% significance level was employed), and weighted average (WA) scores were employed for the response variables. For partial RDA, a preliminary stage was performed in which the explanatory variables (thyroid status, both with and without serum T4 and TSH biomarker concentrations and/or BMI, age and gender) table was sub-divided into two groups, the first of which [X(1)] contained conditioning variables (BMI, age and gender), the effect of which was removed, since their effects on BP components are already known). Regressions were then performed on the Y (blood pressure) and X(2) (thyroid status, both with and without serum TSH and T4 levels) tables, and the residuals of the regressions arising were then employed for the RDA step. In this manner, we analysed the effects of the second [X(2)] group of variables, i.e. that remaining after the effect of the first [X(1)] group of conditioning variables had been removed.

Canonical correlation analysis (CCA) was also performed using XLSTAT software and a minimum filter factor of 80%, as was principal component analysis (PCA). PCA was conducted both with and without a subsequent Varimax rotation (the latter with Kaiser normalisation and a maximum of 4 components), and the application of Bartlett's

sphericity test. Datasets were standardised prior to the performance of both CCA and PCA analysis.

4.2. Results

4.2.1. Descriptive statistics

The overall mean age for hyperthyroid, hypothyroid and euthyroid control patients were 35.59 yr.; 34.15 yr.; and 38.40 yr.; respectively. The range and mean values of BP components for hyperthyroid, hypothyroid and euthyroid control patients were SBP: 108 to 150, and 127.04 mmHg; 80 to 200, and 120.31 mmHg; 90 to 160, and 115.04 mmHg; respectively. DBP: 48 to 92, and 77.80 mmHg; 60 to 140, and 80.59 mmHg; 70 to 100, and 77.28 mmHg respectively; MAP: 68.67 to 110.00, and 94.04 mmHg; 73.33 to 160.00, and 93.83 mmHg; 76.67 to 120, and 89.87 mmHg respectively. SBP:DBP ratio: 1.3750 to 2.2917, and 1.637; 1.1429 to 1.8333, and 1.495; 1.1250 to 1.8286, and 1.492 respectively.

Similarly, the range and mean BMI values for hyperthyroid, hypothyroid and euthyroid control patients were 14 to 21, and 17.71 $kg.m^{-2}$; 13 to 33, and 22.39 $kg.m^{-2}$; 16 to 24, and 21.38 $kg.m^{-2}$ respectively. The range and mean values of serum thyroid disease biomarkers for hyperthyroid, hypothyroid and control euthyroid patients were TSH: 0 to 0.13, and 0.085 IU/ml; 26.00 to 100.00, and 75.00 IU/ml; 0.10 to 5.10, and 2.07 IU/ml respectively. T4: 160.00 to 240.00, and 198.52 ng/ml; 50.00 to 113.00, and 65.53 ng/ml; 55.00 to 147.00, and 96.34 ng/ml respectively.

4.2.2. Univariate Statistical Analysis

ANOVA of the dataset revealed very highly significant differences between the disease classifications for (1) SBP, the mean values [Figure 4.1(a)] being in the order Hyperthyroid >> Hypothyroid > Euthyroid ($p < 0.0001$); (2) DBP, the mean value [Figure 4.1(b)] order being Hypothyroid > Hyperthyroid ≅ Euthyroid ($p < 0.0001$); (3) SBP:DBP ratio, the mean value [Figure 4.1(c)] order being Hyperthyroid >> Hypothyroid ≅ Euthyroid ($p < 0.0001$); (4) MAP, the mean value [Figure 4.1(d)] order being Hyperthyroid ≅ Hypothyroid >> Euthyroid ($p < 0.0001$); and finally (5) BMI, the mean value [Figure 4.1(e)] order being Hypothyroid > Euthyroid >> Hyperthyroid ($p <0.0001$). The mean serum TSH [Figure 4.1(f)] and T4 [Figure 4.1(g)] levels were in the order hypothyroid >> euthyroid >> hyperthyroid ($p < 0.0001$), and hyperthyroid >> euthyroid >> hypothyroid ($p < 0.0001$) respectively (Table 4.1).

Figure 4.1 (a) Univariate statistical analysis – systolic blood pressure

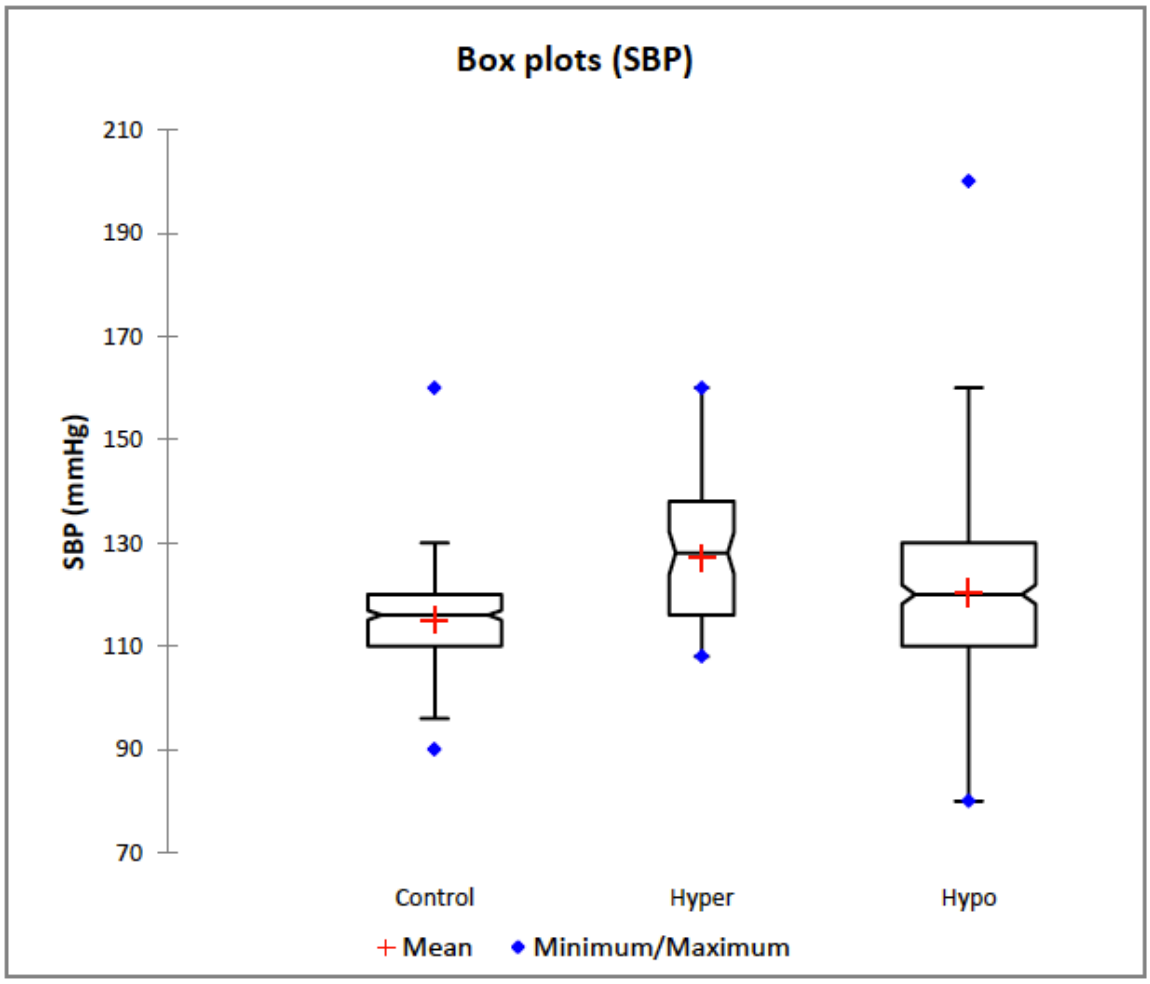


Figure 4.1 (b) Univariate statistical analysis – diastolic blood pressure

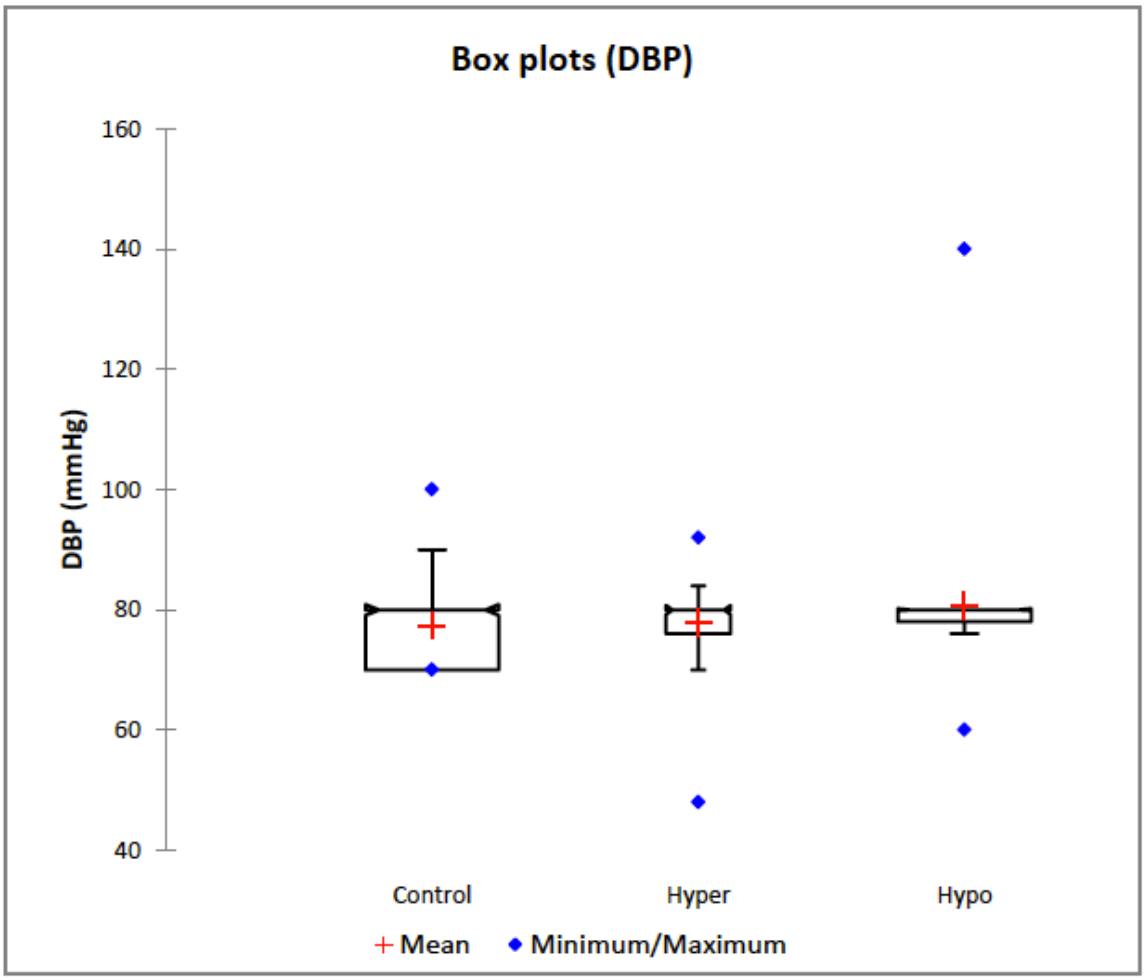


Figure 4.1 (c) Univariate statistical analysis – SBP/DBP (systolic blood pressure: diastolic blood pressure ratio)

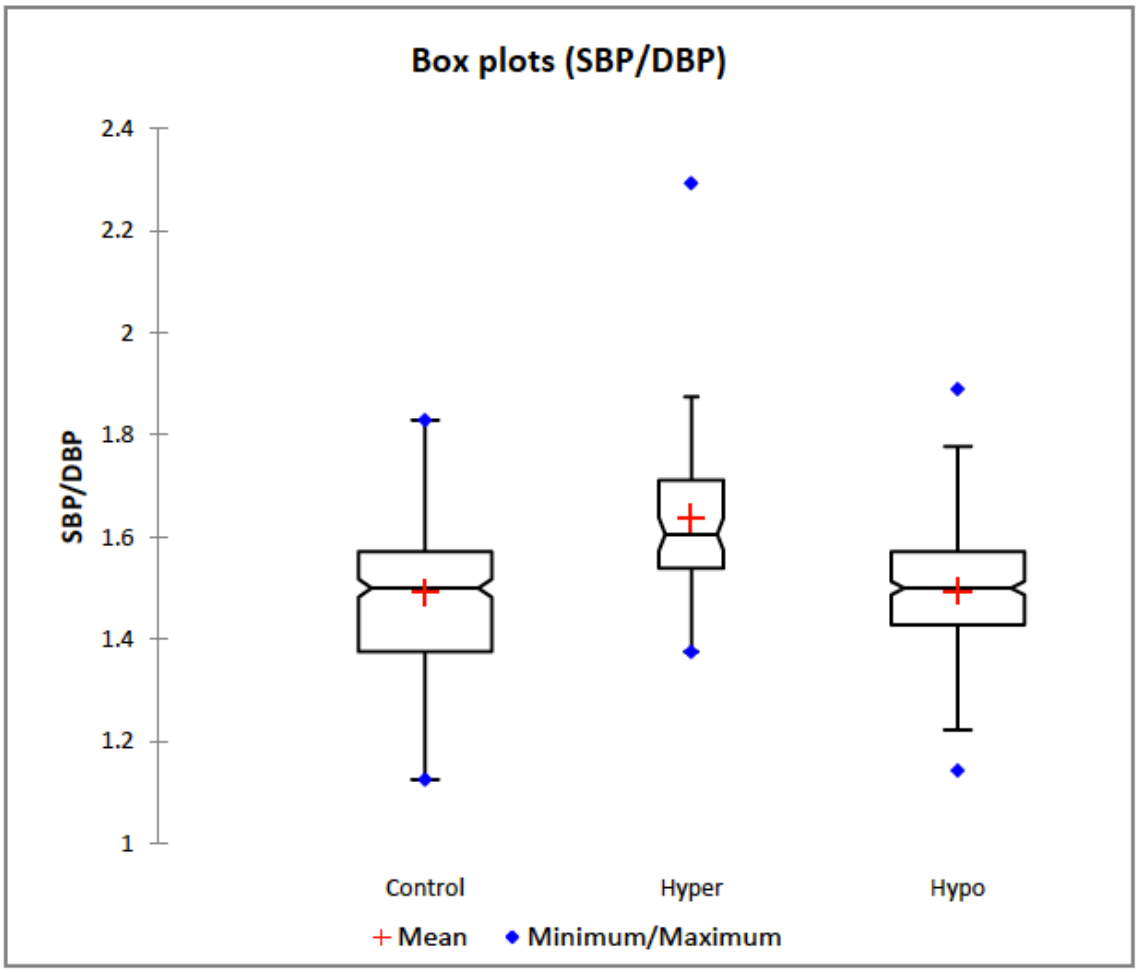


Figure 4.1 (d) Univariate statistical analysis – mean arterial pressure

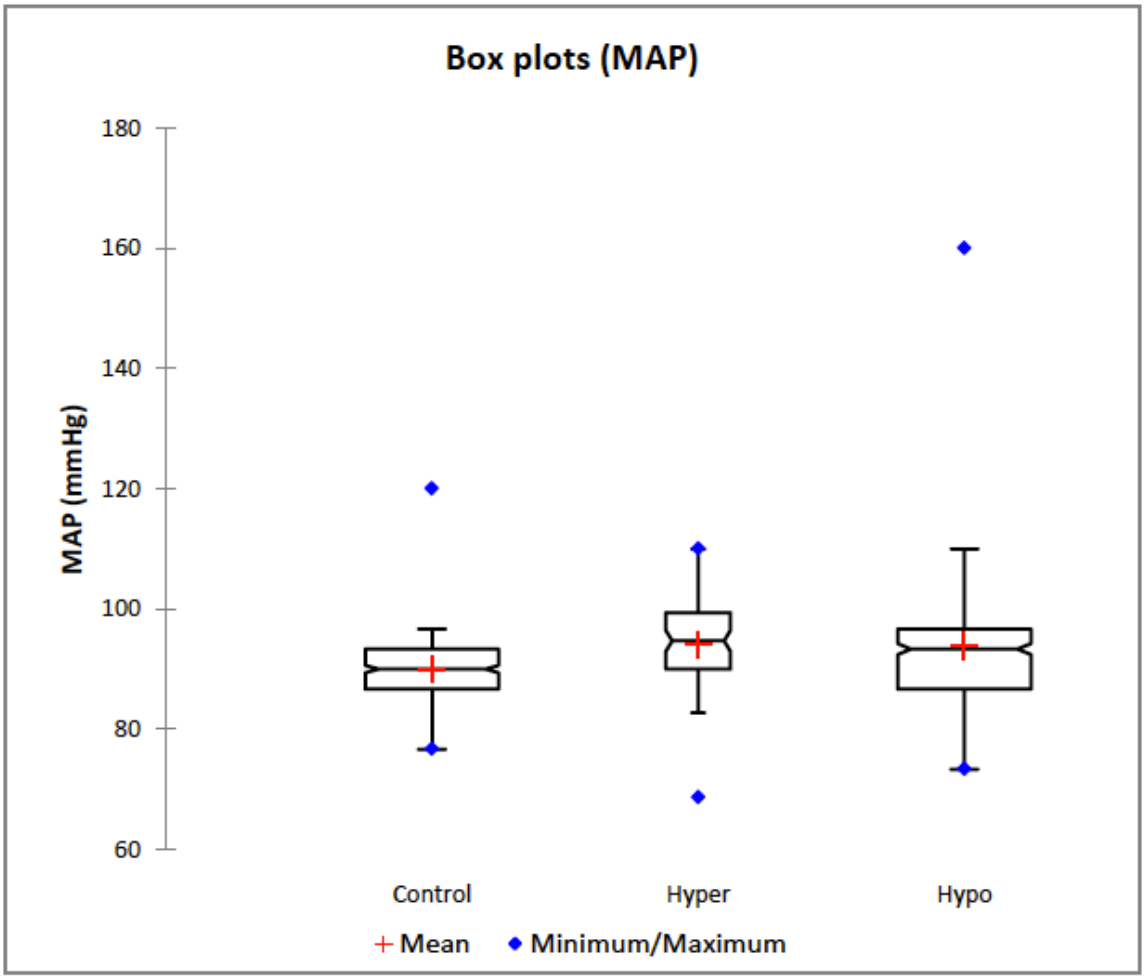


Figure 4.1 (e) Univariate statistical analysis – body mass index

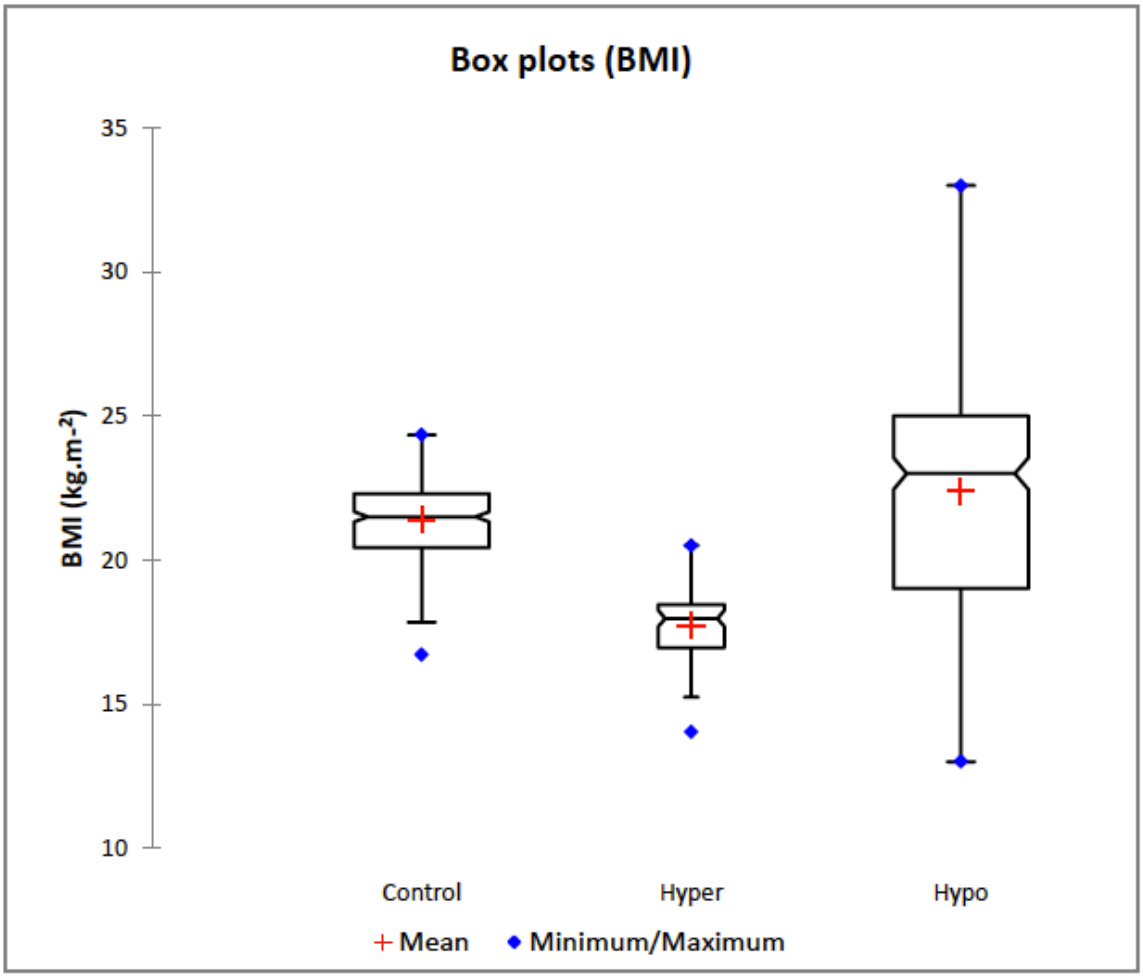


Figure 4.1 (f) Univariate statistical analysis – TSH

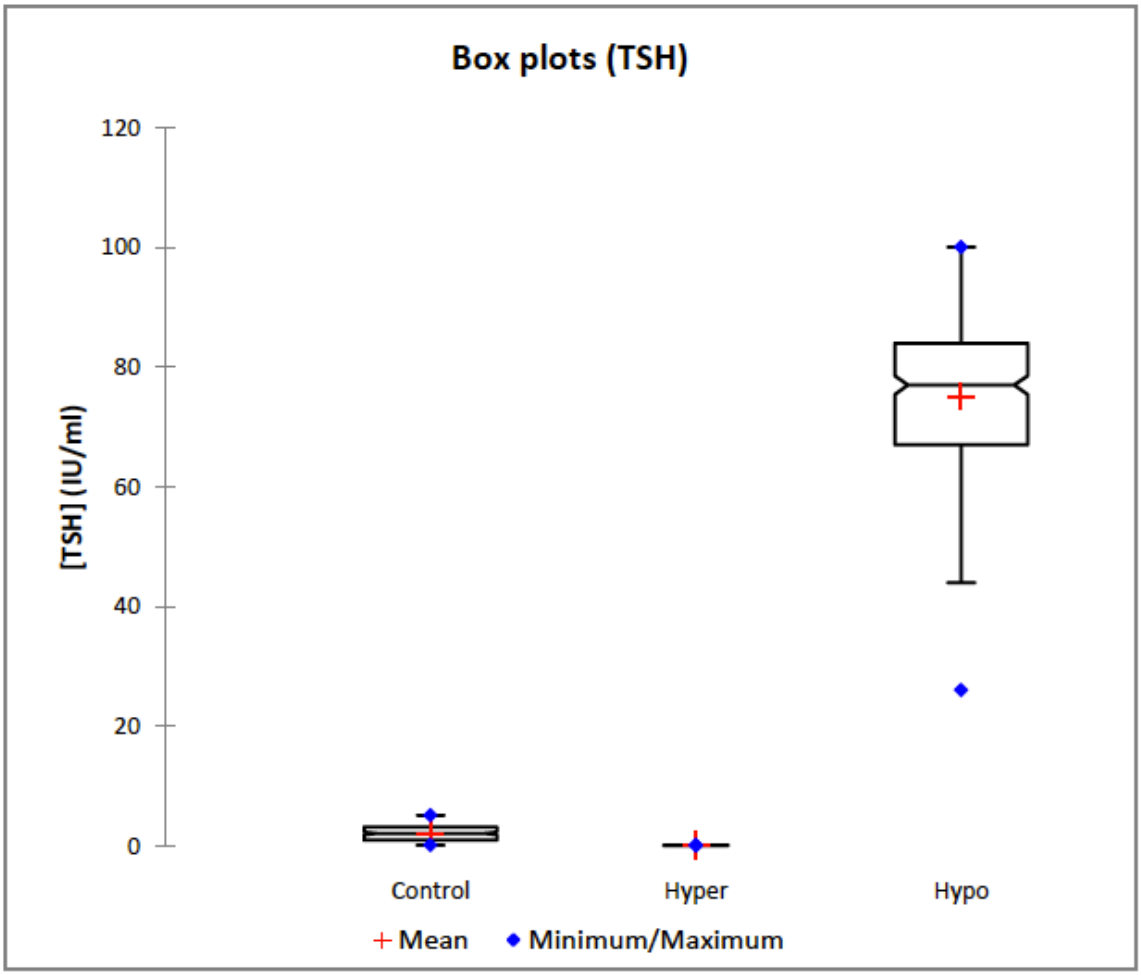


Figure 4.1 (g) Univariate statistical analysis – T4

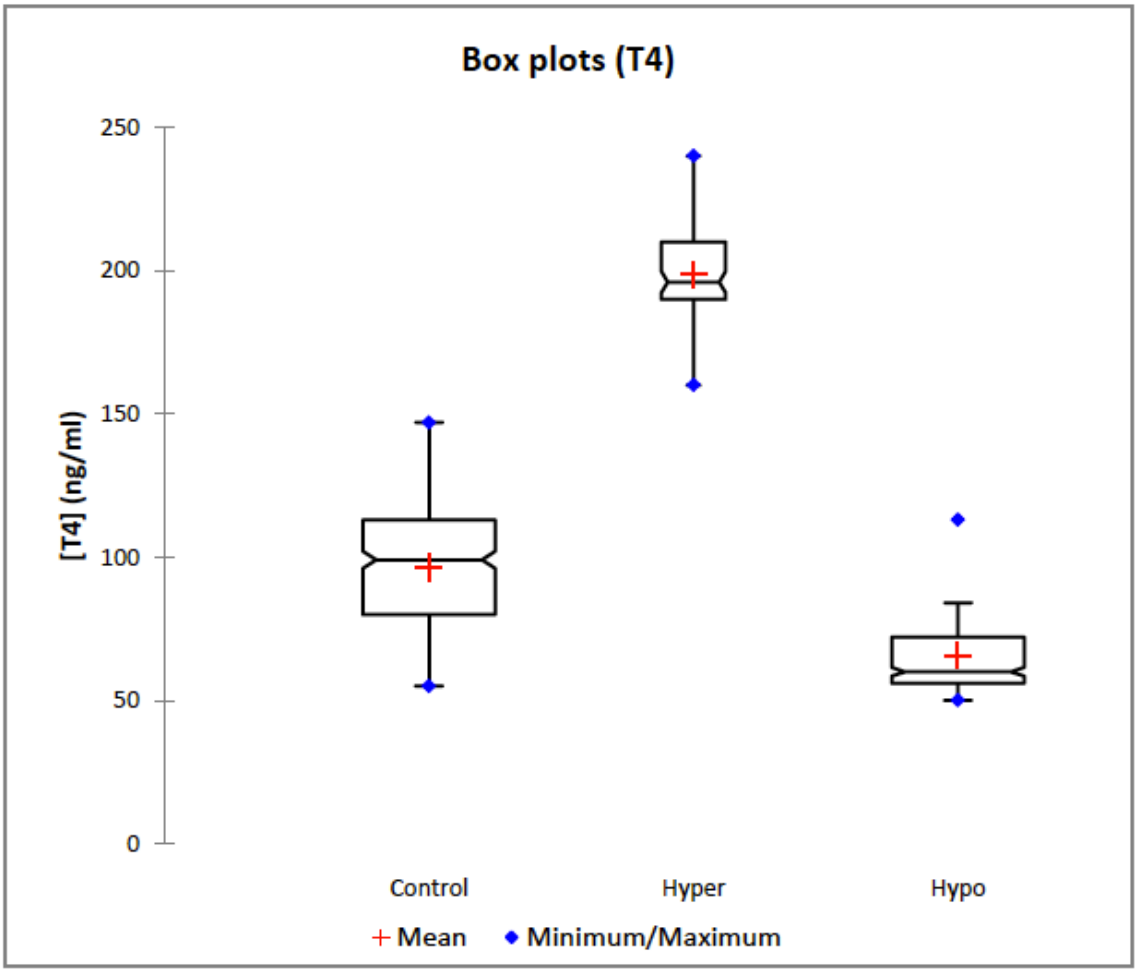


Table 4.1. Mean ± 95% confidence intervals (CIs) for SBP, DBP, SBP:DBP ratio, MAP, BMI, T4 and TSH level, and Age parameters determined for Hypothyroid (n = 300), Hyperthyroid (n = 71) and Euthyroid (n = 300) patients. The significance of differences between the mean values of the three thyroid status classifications were determined by ANOVA (Section 2).

Parameter	Thyroid Status	Mean ± 95% CIs	p Value Euthyroid vs. Hypothyroid	p Value Euthyroid vs. Hyperthyroid	p Value Hypothyroid vs. Hyperthyroid
SBP (mmHg)	Hypothyroid	120.31 ± 1.79	< 0.0001	< 0.0001	0.00016
	Hyperthyroid	127.04 ± 3.30			
	Euthyroid	115.04 ± 1.13			
DBP (mmHg)	Hypothyroid	80.59 ± 1.00	< 0.0001	Ns	0.002
	Hyperthyroid	77.80 ± 1.46			
	Euthyroid	77.28 ± 0.59			
SBP:DBP Ratio	Hypothyroid	1.495 ± 0.014	ns	< 0.0001	< 0.0001
	Hyperthyroid	1.637 ± 0.040			
	Euthyroid	1.492 ± 0.015			
MAP (mmHg)	Hypothyroid	93.83 ± 1.19	< 0.0001	< 0.0001	Ns
	Hyperthyroid	94.04 ± 1.77			
	Euthyroid	89.87 ± 0.65			
BMI (kg.m-2)	Hypothyroid	22.39 ± 0.42	< 0.0001	< 0.0001	< 0.0001
	Hyperthyroid	17.71 ± 0.32			
	Euthyroid	21.38 ± 0.16			
Serum T4 level (ng/ml)	Hypothyroid	65.53 ± 1.32	< 0.0001	< 0.0001	< 0.0001
	Hyperthyroid	198.52 ± 4.04			
	Euthyroid	96.34 ± 2.54			
Serum TSH level (IU/ml)	Hypothyroid	75.00 ± 1.94	< 0.0001	Ns	< 0.0001
	Hyperthyroid	0.085 ± 0.008			
	Euthyroid	2.073 ± 0.164			
Age (yr.)	Hypothyroid	34.15 ± 1.37	0.002	Ns	Ns
	Hyperthyroid	35.59 ± 2.75			
	Euthyroid	38.36 ± 1.54			

Abbreviations: ns, not significant. BMI – body mass index, MAP – mean arterial pressure, SBP – systolic blood pressure, DBP – diastolic blood pressure, T4 and TSH – thyroid hormones

As expected, analysis of the untransformed datasets revealed that there were also highly significant differences between the variances ('scatter') of these BP components between thyroid status groups, for example Hypothyroid ≅ Hyperthyroid >> Euthyroid for SBP ($p < 0.0001$); Hypothyroid >> Hyperthyroid > Euthyroid for DBP ($p < 0.0001$); Hyperthyroid >> Hypothyroid ≅ Euthyroid for SBP:DBP ratios ($p = 0.005$); and Hypothyroid >> Hyperthyroid > Euthyroid for MAP ($p < 0.0001$). Interestingly, the variance of the BMI values of the hypothyroid patient group was found to be much greater than those of both the euthyroid and hyperthyroid patient groups ($p < 0.0001$).

Focusing on the SBP:DBP ratio in view of the clear, highly significant differences in this parameter between the disease classification groups, further univariate analysis was performed. An ANCOVA model without allowing for any interaction effects demonstrated that there were extremely highly significant differences between Disease Classifications ($p < 0.0024$), again predominantly ascribable to the much higher SBP:DBP ratio of hyperthyroid patients than those of hypothyroid and euthyroid status, and also that serum T4 and TSH concentrations exerted highly significant effects as covariates ($p < 0.0001$ and 0.00572 respectively) on this BP component; all further (explanatory) covariates, i.e. BMI values, age and gender, were found to not exert a significant influence on this (dependent) SBP:DBP ratio variable. Standardised regression coefficients (and the sign of these contributions) for each of the significant covariates in this model were in the order

hyperthyroid status (+) > euthyroid status (-) > hypothyroid status (-) > serum TSH level (-) > serum T4 level (+), i.e. there were positive and negative contributions of serum T4 and TSH concentrations towards the SBP:DBP ratio dependent variable, as expected. ANCOVA performed with allowance for all possible first-order interaction effects demonstrated that the serum TSH level-thyroid status interaction component of variance was extremely significant ($p < 0.0001$), with also a significant effect for the serum T4-TSH concentrations interaction effect ($p = 0.01024$).

Figure 2 exhibits plots of BMI versus age, and SBP:DBP ratio, MAP, and serum TSH and T4 levels versus BMI. Also shown are plots of SBP:DBP ratio versus BMI, serum T4 and serum TSH concentrations. The plot of BMI versus age revealed at least some distinction between the euthyroid and hyperthyroid groups [Figure 4.2(a)], as did that of MAP versus BMI [Figure 4.2(b)]. However, the plot of serum TSH level versus BMI [Figure 4.2(c)] shows a high level of discrimination between all three thyroid status classifications, whereas there was also a very clear separation visible between the hyperthyroid and both the euthyroid and hypothyroid groups (with also at least some distinction between these latter two groups) in the plot of serum T4 level versus BMI [Figure 4.2(d)]. Plots of SBP:DBP ratio versus BMI [Figure 4.2(e)] clearly showed that hyperthyroid patients had a very significantly higher SBP:DBP ratio and lower mean BMI values than those of both healthy control and hypothyroid patients. Moreover, particularly notable was the observation that plots of SBP:DBP ratio versus serum T4 and TSH concentrations [Figures 4.2(f) and 4.2(g) respectively] exhibited high levels of distinction between the three thyroid disease status classifications.

Figure 4.2 (a) ANCOVA – body mass index versus age

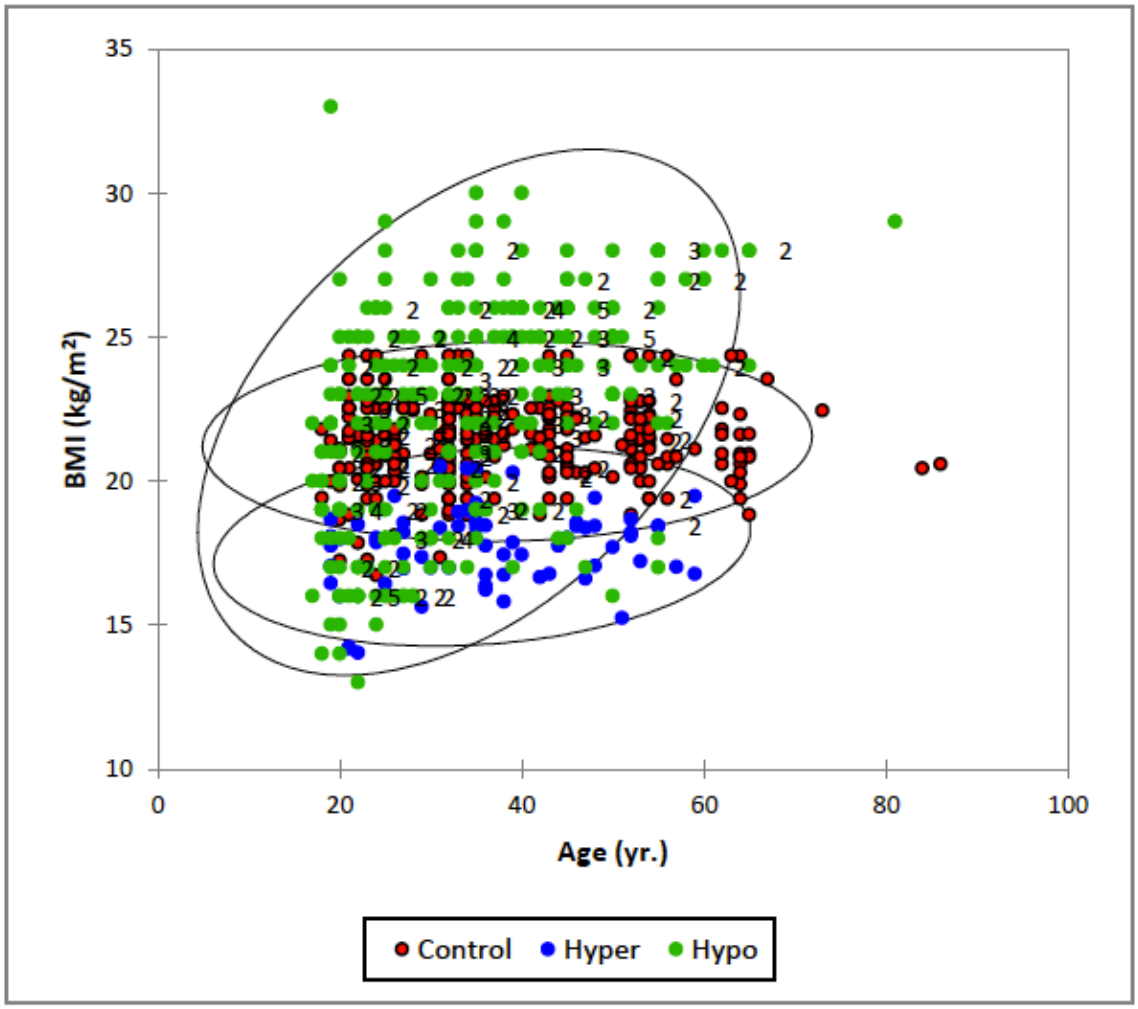


Figure 4.2. (b) ANCOVA – mean arterial pressure versus body mass index

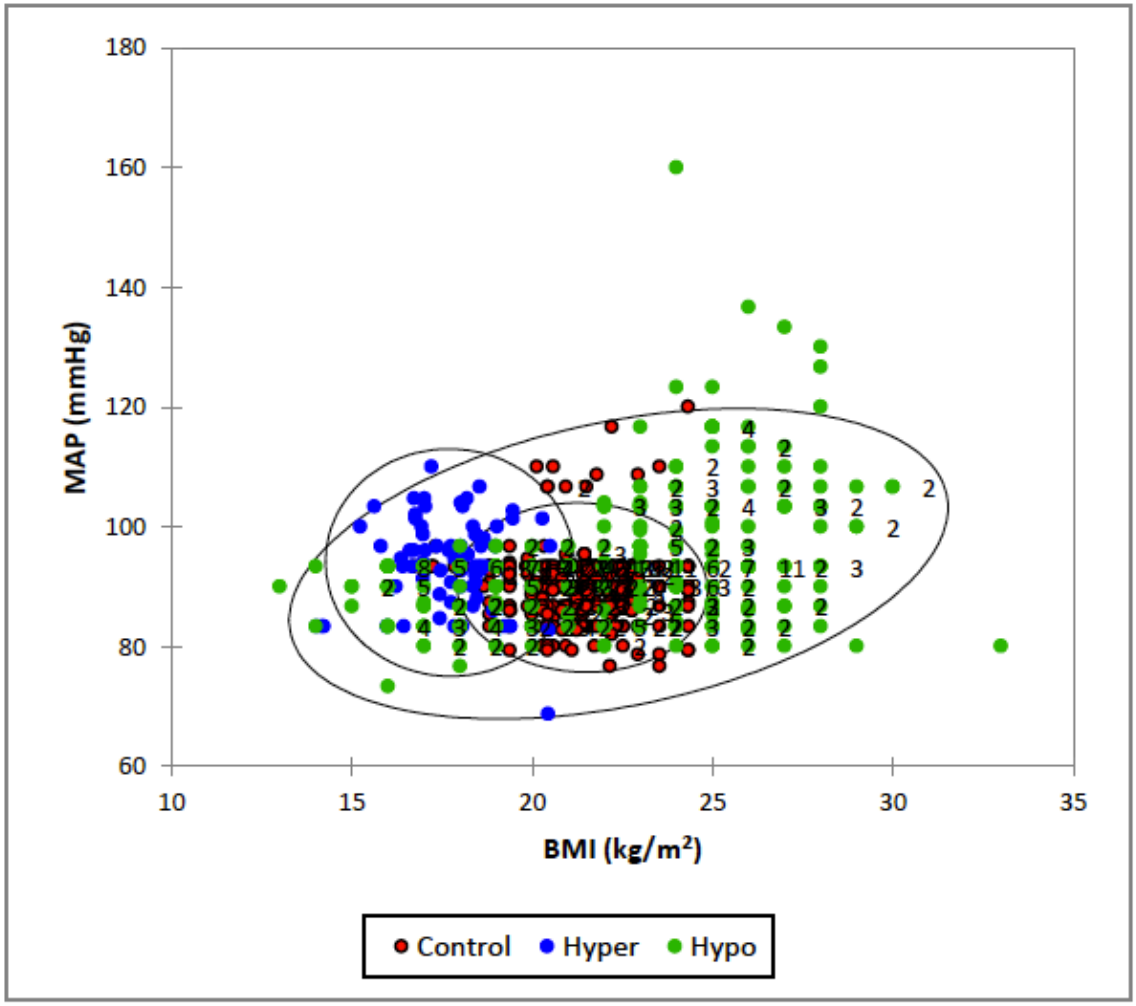


Figure 4.2 (c) ANCOVA – serum TSH level versus body mass index

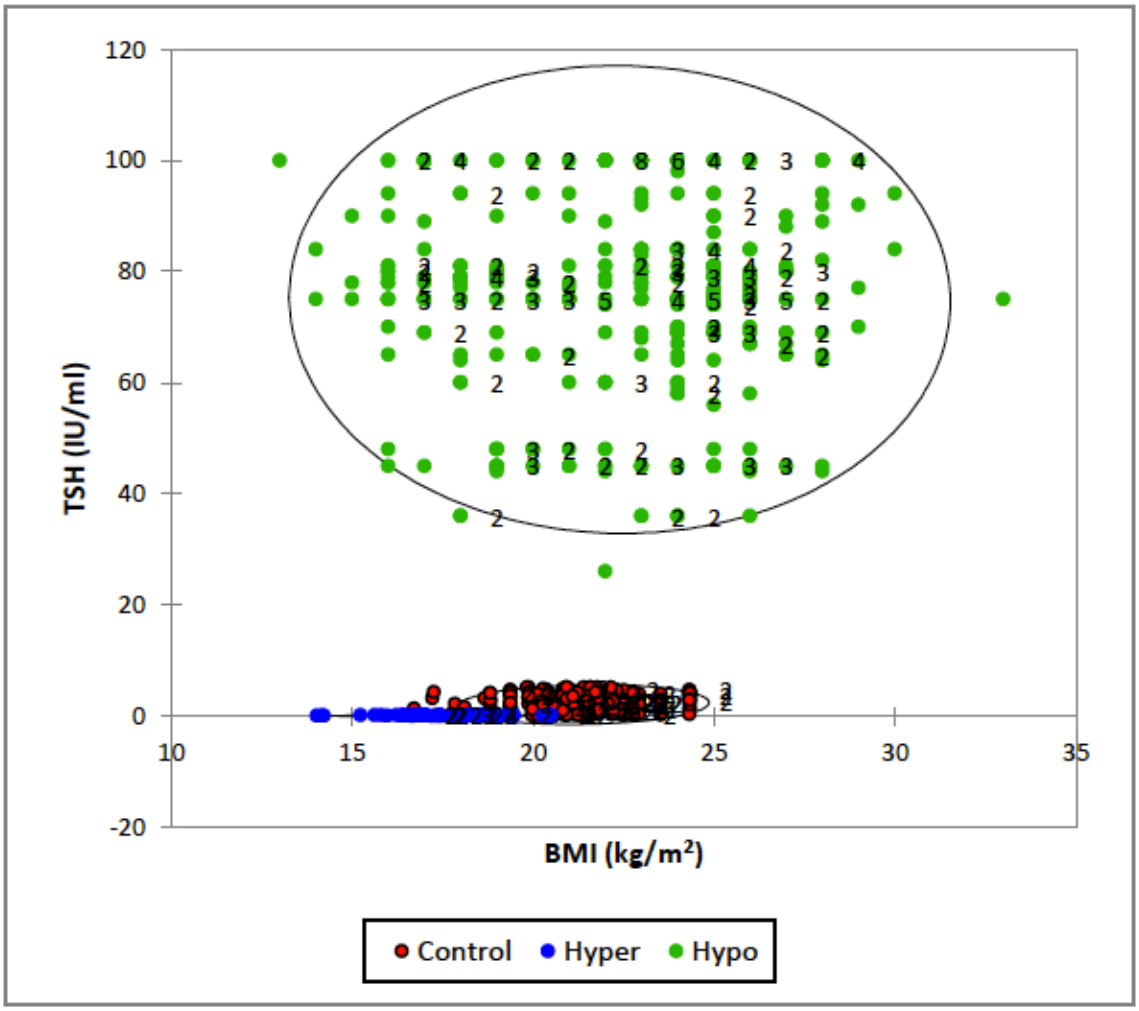


Figure 4.2 (d) ANCOVA – serum T4 level versus body mass index

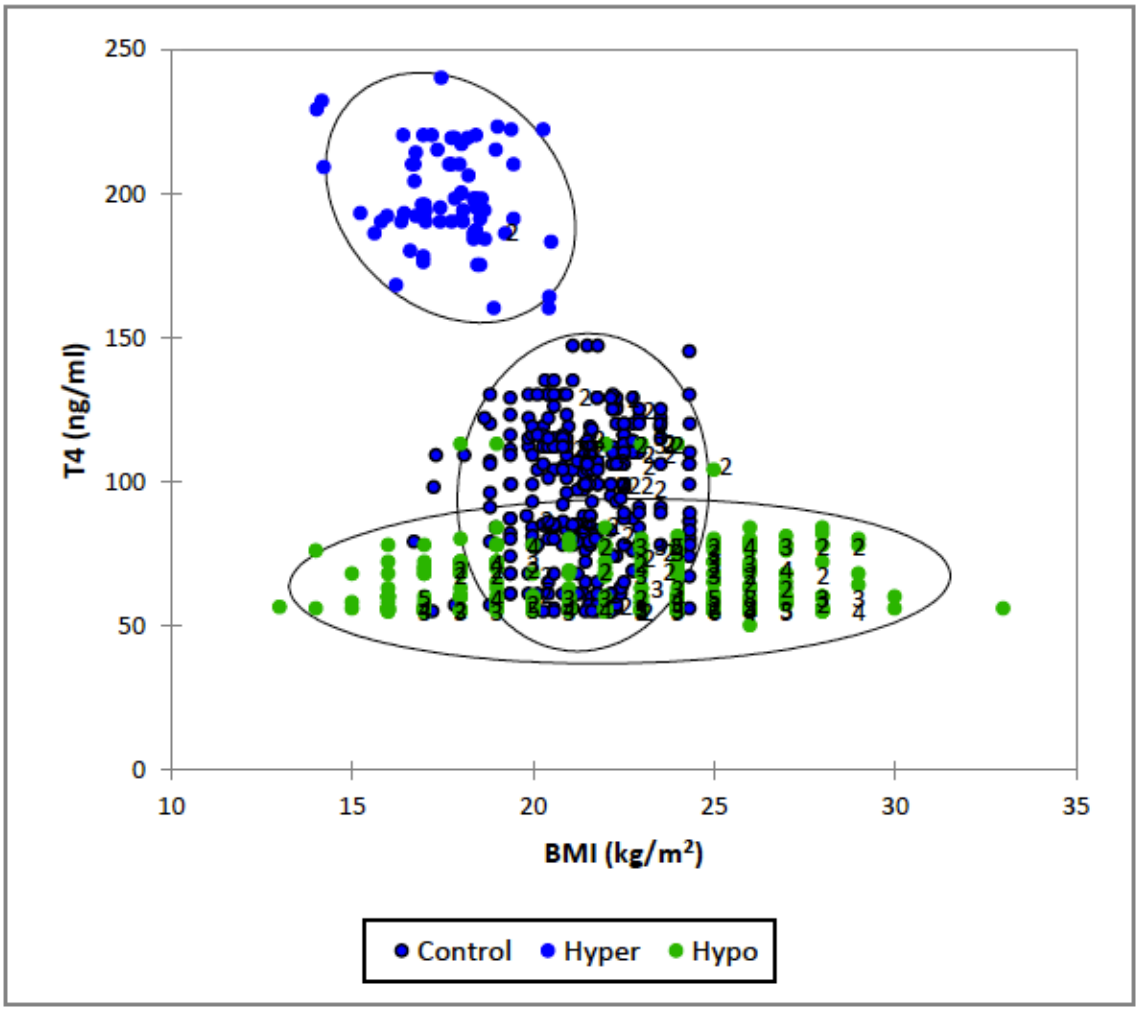


Figure 4.2 (e) ANCOVA – SBP/DBP (systolic blood pressure: diastolic blood pressure ratio) versus body mass index

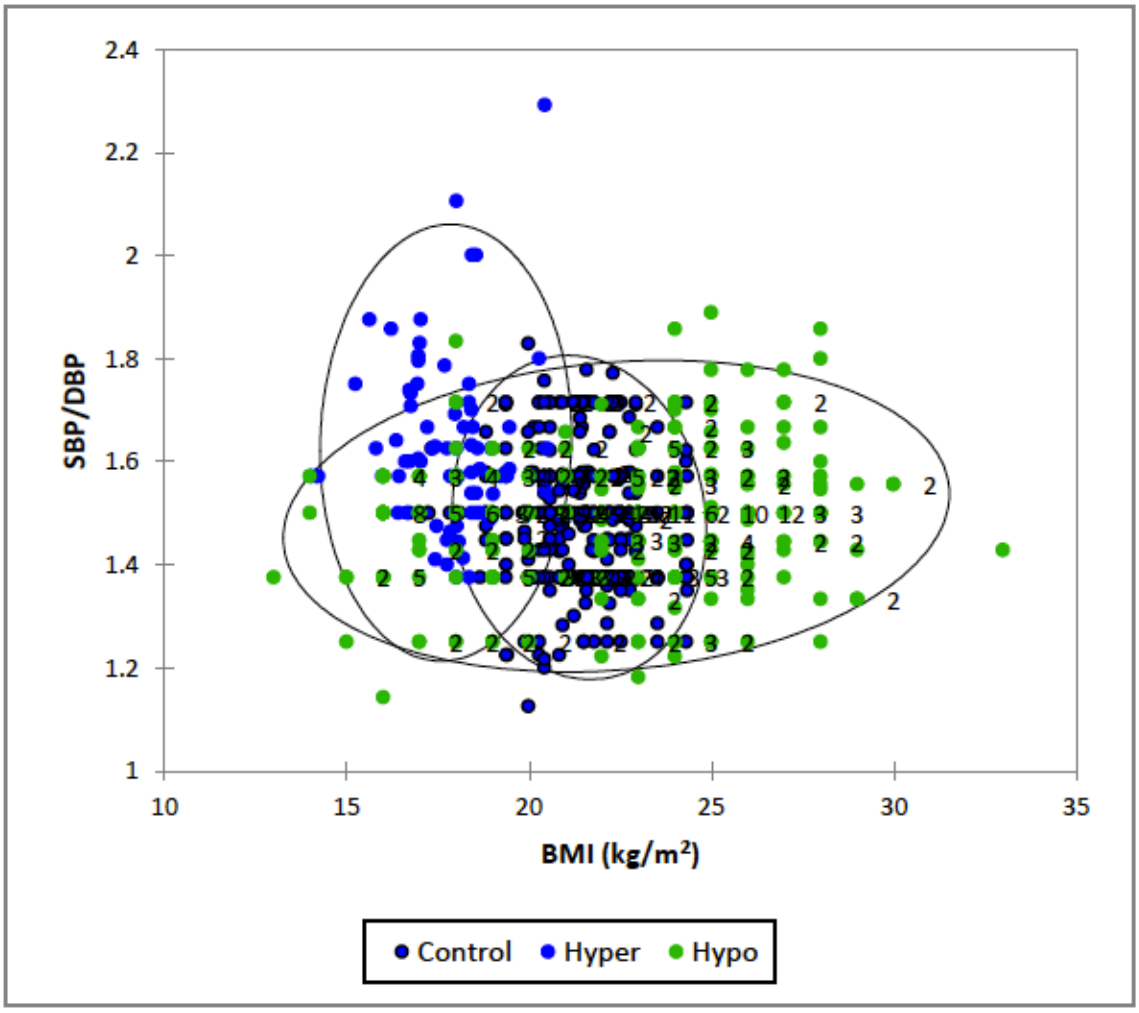


Figure 4.2 (f) ANCOVA - SBP/DBP (systolic blood pressure: diastolic blood pressure ratio) versus serum T4 level

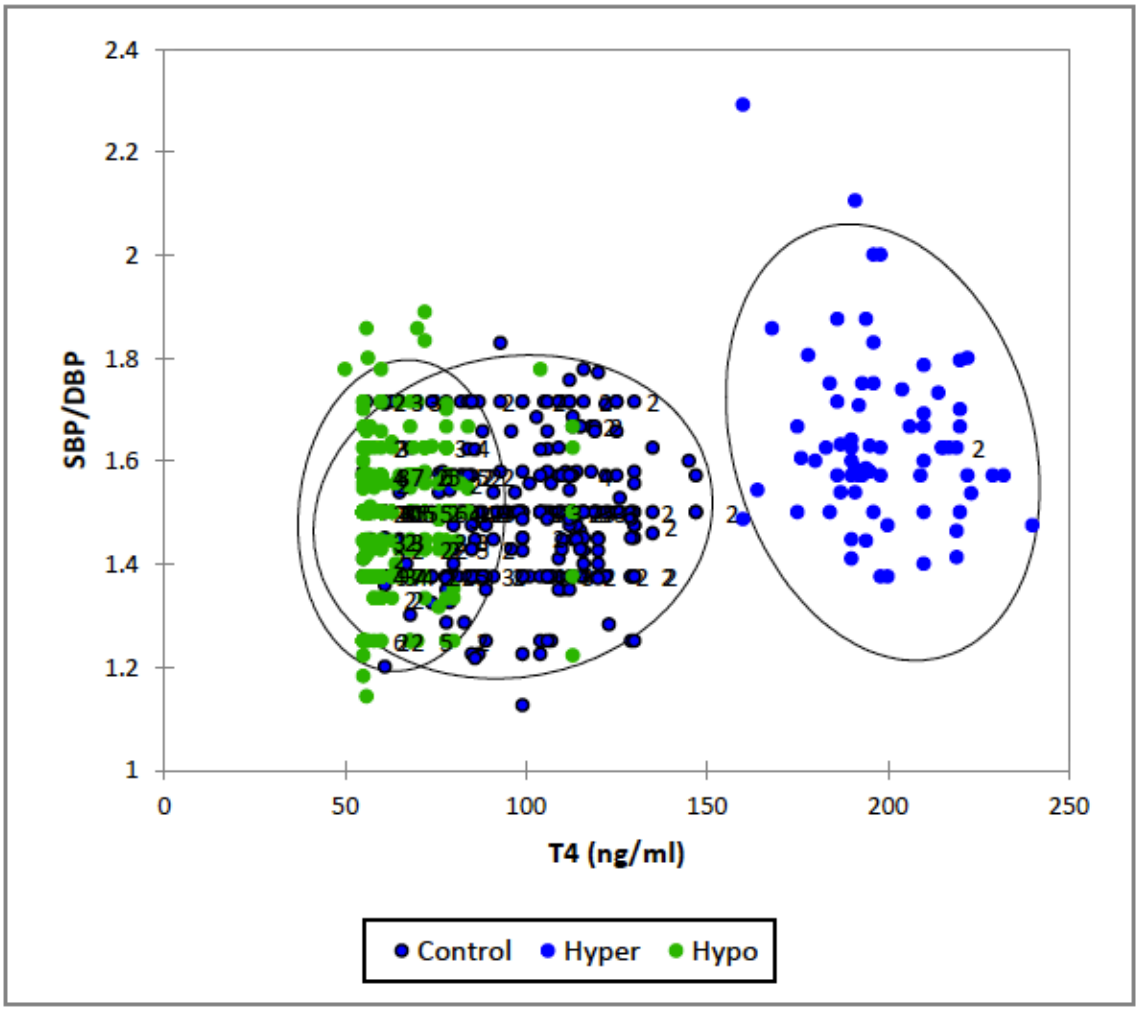
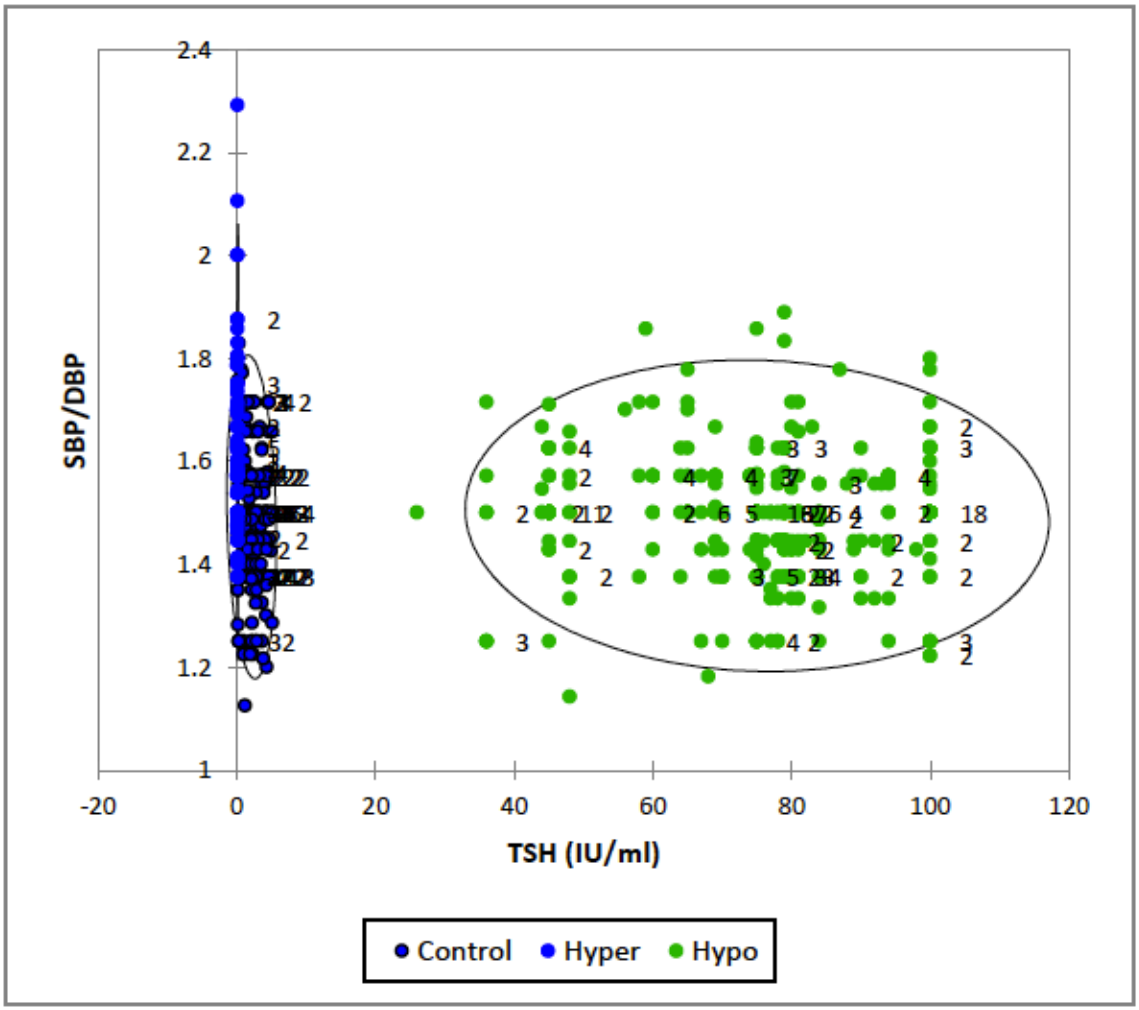


Figure 4.2 (g) ANCOVA - SBP/DBP (systolic blood pressure: diastolic blood pressure ratio) versus serum TSH level



Based on a BMI threshold cut-off of 23.0, we examined the frequencies of euthyroid and hypothyroid patients within each of the thyroid disease classification groups (< 23 and those with values ≥ 23) via a χ^2 contingency table analysis, and found that there was a very strong association between these two classification criteria [($p < 0.0001$, Monte-Carlo simulation, Figure 4.3(a)], with a much higher proportion of hypothyroid patients in the elevated BMI group [odds ratio of 15.12 (95% CI 9.33-24.50) and a likelihood ratio of 7.26]. Similarly, we also explored the association between this BMI classification and euthyroid vs. hyperthyroid status [Figure 4.3(b)], and also found a significant association between these two criteria ($p = 0.018$), with a PETO odds ratio of 3.72 (95% CIs 1.28-10.87).

Figure 4.3 (a) χ^2 contingency table analysis – body mass index and thyroid status (hypothyroidism versus euthyroid)

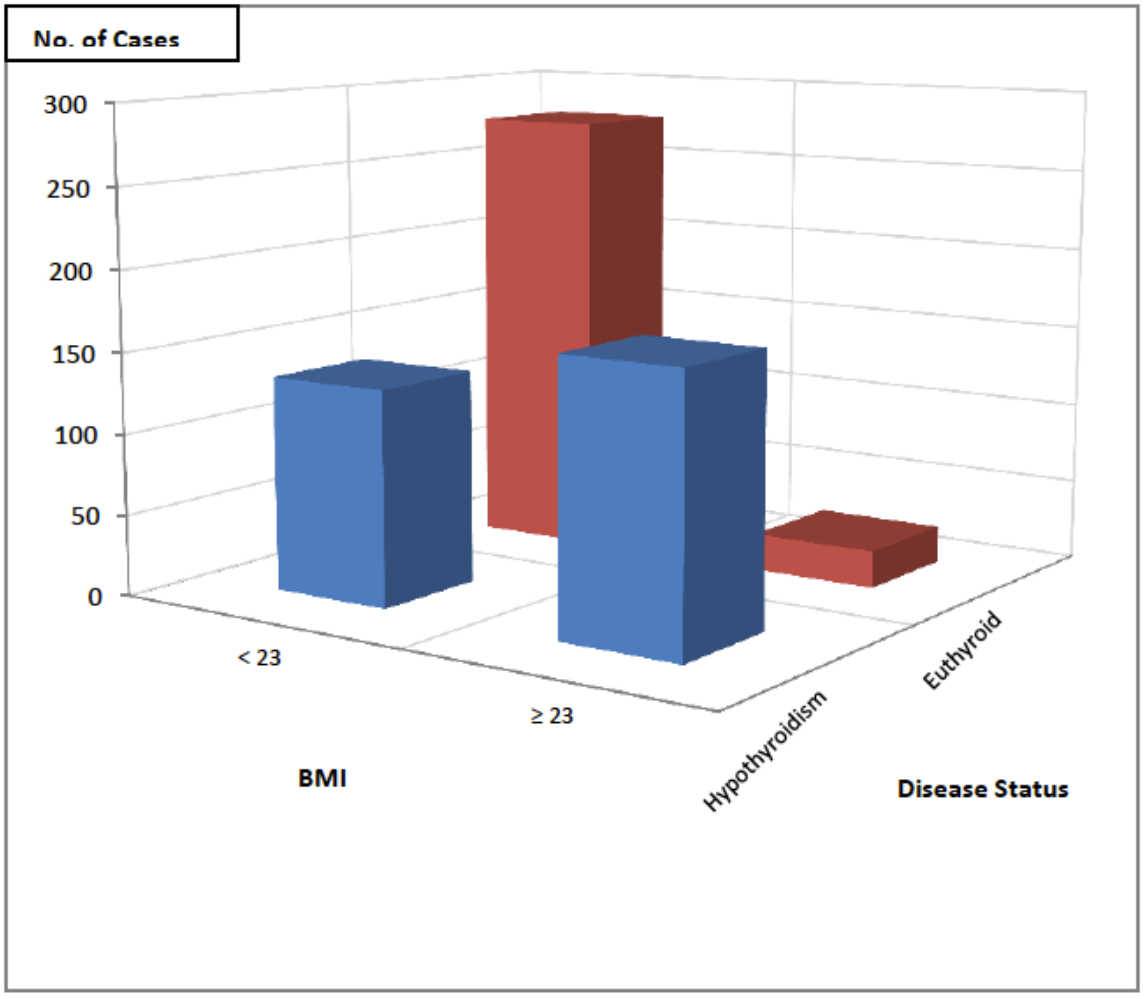
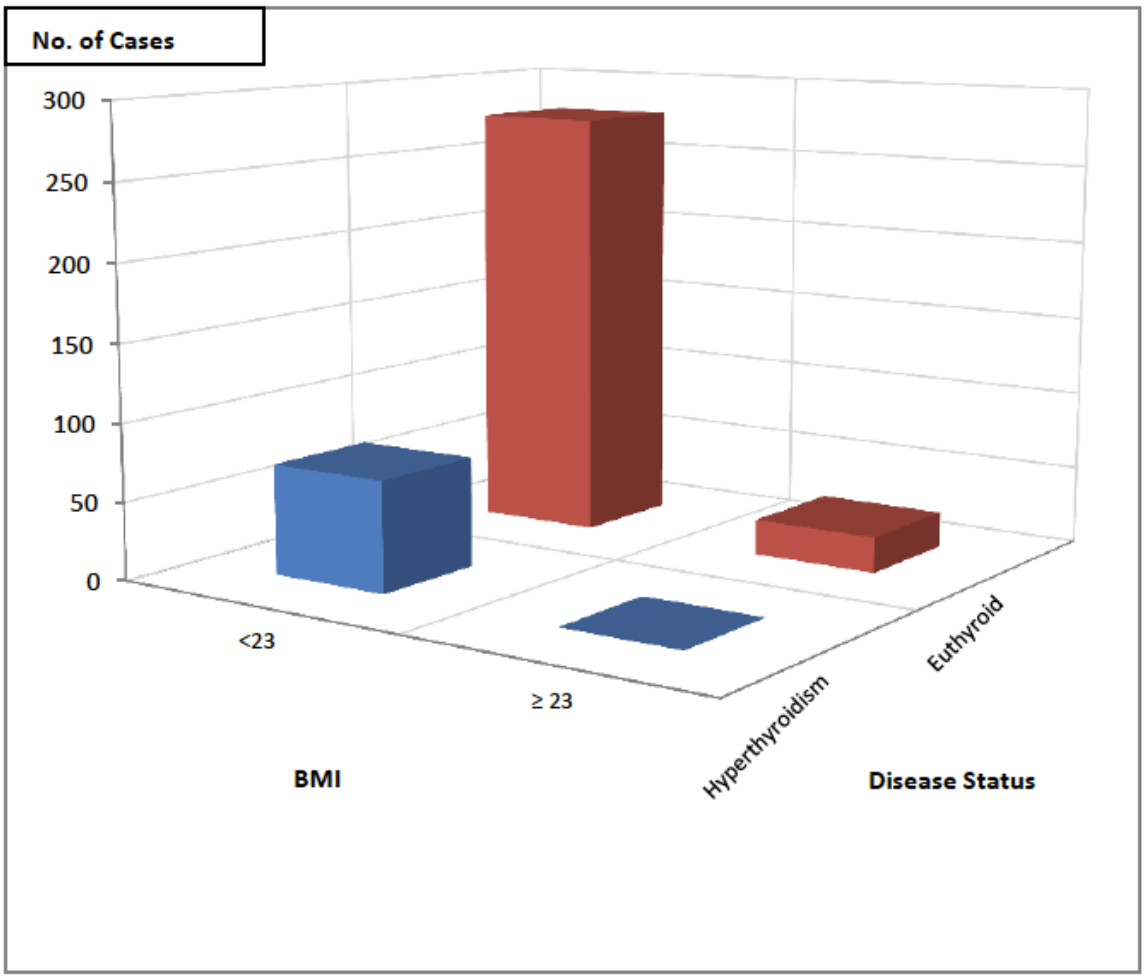


Figure 4.3 (b) χ^2 contingency table analysis – body mass index and thyroid status (hyperthyroidism versus euthyroid)



4.2.3 Multivariate Statistical Analysis

Partial Correlation Analysis

We employed partial correlation analysis in order to explore similarities/dissimilarities between a MV dataset (consisting of patient serum T4 and TSH biomarker levels, BMI and age), and each of the four BP components (SBP, DBP, MAP and SBP:DBP ratio), the latter on an individual basis in view of interfering multicollinearity problems arising from the relatively high positive correlations existing between each of these BP parameters (either previously established or, for the SBP:DBP ratio index, discovered here). Partial correlation was chosen as an optimal method for the investigation of these relationships since it serves to provide realistic representations of relationships between the thyroid status and BP parameters in view of their independence of the influence of (i.e. co-correlations with) further, potentially interfering variables (unlike simple Pearson correlation coefficients). On consideration of the clear 'between-thyroid status' differences in such relationships, we computed partial correlation coefficients [rbp(n).th(1-4)] for each thyroid status classification (Table 4.2).

Table 4.2. Partial correlation coefficient (rbp(n).th(1-4)) values between individual BP components and blood serum TSH and T4 biomarker levels (IU/ml and ng/ml respectively), age (yr.) and BMI ($kg.m^{-2}$) parameters. The corresponding two-tailed significance (p) values of these rbp(n).th(1-4) values are provided in brackets.

Thyroid Disease Status	Parameter	SBP	DBP	MAP	SBP:DBP
Hypothyroid	TSH level	0.1359 (0.0191)	0.1864 (0.00125)	0.1745 (0.00255)	Ns
	T4 level	Ns	ns	Ns	Ns
	Age	0.1939 (0.00078)	0.2144 (0.00020)	0.2194 (0.00014)	
	BMI	0.2589 (< 0.00001)	0.2156 (0.00018)	0.2528 (0.000103)	0.1193 (0.0399)
Hyperthyroid	TSH level	Ns	ns	Ns	Ns
	T4 level	Ns	0.3498 (0.0035)	0.29064 (0.0162)	Ns
	Age	0.3382 (0.0048)	0.3931 (0.00091)	0.40781 (0.00056)	Ns
	BMI	Ns	ns	Ns	Ns
Euthyroid	TSH level	Ns	ns	Ns	-0.1192 (0.0401)
	T4 level	0.1432 (0.0135)	ns	0.1423 (0.0140)	Ns
	Age	Ns	ns	Ns	Ns
	BMI	Ns	ns	Ns	Ns

Abbreviations: ns, not significant. BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, T4 and TSH – thyroid hormones

Although all the rbp(n).th(1-4) values computed are relatively small, approximately one-third of them were statistically significant in view of the very large sample sizes employed in this investigation. Firstly, for the hypothyroid status group of patients, individual SBP, DBP and MAP values all significantly positively correlated with serum TSH concentration, BMI and age, whereas the SBP:DBP ratio index only correlated significantly and

positively with BMI. Secondly, and in contrast, the hyperthyroid status classification exhibited strong positive correlations of the individual DBP and MAP BP components with both the serum T4 level ($p = 0.0035$ and 0.0162 respectively) and age ($p = 0.00091$ and 0.00056 respectively) explanatory variables; the SBP component was only significantly positively correlated with age, and no significant correlations of the SBP:DBP index to any of the explanatory variables were found. Thirdly, for the euthyroid (healthy control) group, significant positive correlations were found between the SBP, DBP and MAP components and serum T4 concentration, whereas, interestingly, a significant negative one was found between the SBP:DBP ratio parameter and serum TSH concentration. These results acquired are at least partially consistent with those acquired from the further MV analysis performed.

Permutation tests via Redundancy Analysis (RDA)

Primarily, we performed a series of permutation tests via RDA in order to explore relationships between BP components and thyroid disease status with its associated serum T4 and TSH biomarker level datasets. This test served to determine whether or not the thyroid status classifications of the study participants is significantly improved over that arising from any other random classification of these groups; the class labels of the euthyroid, hypothyroid and hyperthyroid patients were permuted, and then randomly assigned to different patients. With these 'incorrect' disease class labels, a classification model was again computed; hence, the rationale was that with these 'incorrect' class labels, the computed model for classification purposes should be ineffective at class prediction (since the groups are generated randomly, the null hypothesis is that there are no

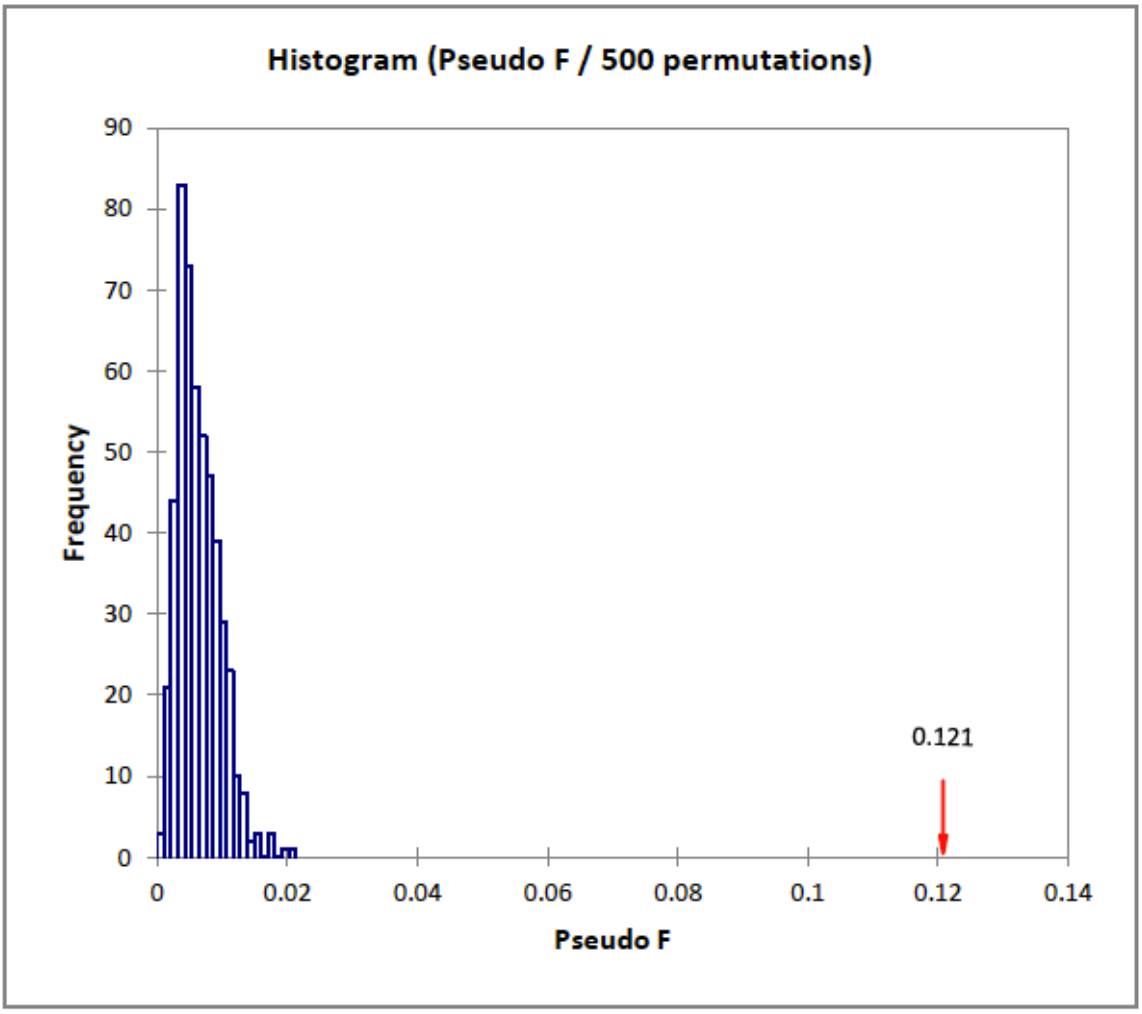
differences between them). With repetition of this permutation test many times (500, 1,000 or 2,000 times in this investigation), a null distribution of classifications which are expected to be insignificant were formed, and if the computed statistic (pseudo-F) lies outside at least the 95% or 99% confidence bounds of this distribution, then it could be concluded that there is a significant (linear) relationship between the two sets of parameters.

In this manner we utilised four experimental models: (1) a full RDA in which relationships between all BP components (SBP, DBP, SBP:DBP ratio and MAP values as response variables) to all thyroid status classifications (hyper and hypothyroid, and euthyroid) and biomarkers (serum T4 and TSH levels), together with BMI, age and gender as explanatory variables; (2) a partial RDA in which the conditioning effects of the BMI, age and gender variables were removed from model (1); (3) a somewhat simpler full RDA model in which all of the above BP components served as response variables, and only the thyroid status classification was employed as the explanatory variable; and (4), as (3), but a partial RDA in which the conditioning effects of the BMI, age and gender variables were again removed.

Extremely highly significant relationships were found for all of the above four experimental models ($p < 0.0001$), results which clearly demonstrated powerful associations between thyroid disease status and each of the four BP components examined (Figure 4.4). Indeed, for model (1), only the first and second factors significantly contributed to the total variance (80 and 20%, respectively), and the order of each factorial

contribution for the explanatory variables was euthyroid disease status > BMI > age > serum TSH level > hypothyroid disease status > gender for factor 1, and hyperthyroid disease status and serum T4 level for factor 2, i.e. the second component was ascribable to the hyperthyroid condition [these two factors represent linear combinations of (correlated) quantitative explanatory variables and are orthogonal (uncorrelated) to each other]. For the BP component (response) variables, however, contributions to factor 1 were MAP > SBP > DBP values, whereas, as expected, only the SBP:DBP ratio (highly significantly elevated in hyperthyroid patients over those in the hypothyroid and euthyroid classifications) contributed to the second factor.

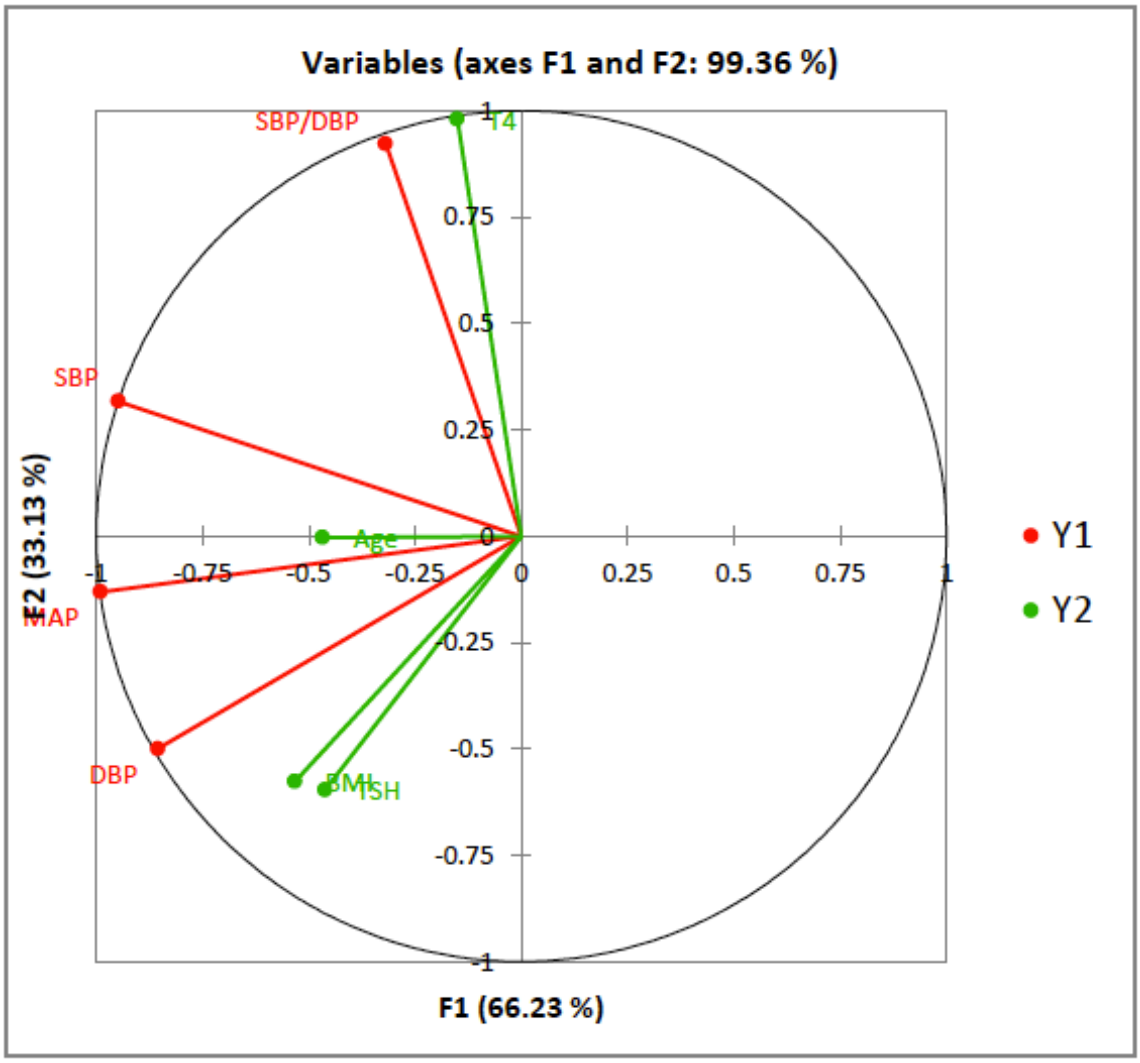
Figure 4.4 Partial RDA permutation test



Canonical Correlation Analysis (CCA)

CCA analysis performed on the complete centered/reduced datasets revealed that there was an extremely strong relationship between the quantitative thyroid disease classification variables (blood plasma T4 and TSH levels, together with age and BMI values) and the BP component dataset (SBP, DBP, SBP:DBP ratio and MAP values $p < 0.0001$), which featured two significant factors (Wilks'-Lambda test), and hence there were two highly statistically significant dimensions between these two sets of variables (Figure 4.5). As noted above for the RDA conducted, BP variables contributing to factor 1 were MAP (correlation -0.990) > SBP (-0.948) > DBP (-0.855) values, whereas only the SBP:DBP ratio contributed significantly to factor 2 (correlation 0.922). There was also a notable canonical correlation between the SBP:DBP ratio parameter and serum T4 concentration, the latter also exhibiting a very strong positive correlation to factor 2 (0.980). Age was strongly negatively and positively correlated to factor 1 and MAP values respectively, and there was a moderate positive correlation between this variable and BMI values. However, BMI was negatively correlated to both factors 1 and 2, and there was also a strong positive correlation between this variable and serum TSH concentrations, which presumably arises from the highly significantly greater BMI values of the hypothyroid status class of patients.

Figure 4.5 Canonical correlation analysis



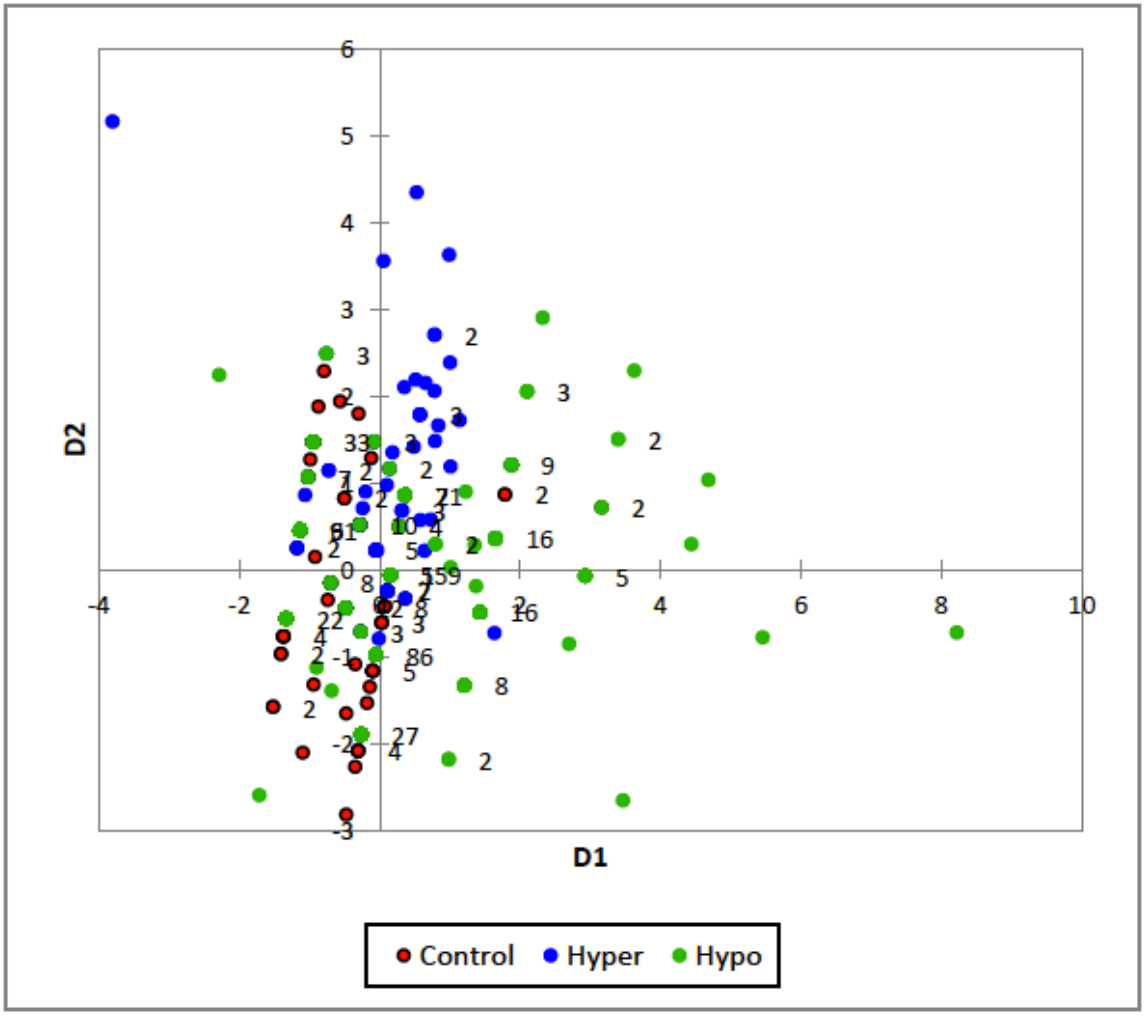
Overall, the correlations between the explanatory variables significantly contributing to factor 1 were in the order BMI > age ≅ serum TSH level, and that exerting an influence, albeit a substantial one, on factor 2 was only serum T4 concentration (the correlation of this variable with the second canonical dimension was 0.98). These results demonstrate that the second canonical dimension is ascribable to the hyperthyroid status classification, results which are entirely consistent with those acquired by RDA.

CCA was also performed on the individual thyroid status patient groups; as expected, relationships between the above quantitative thyroid disease classification variables and the BP component dataset were found to be significant for only the hypo and hyperthyroid status classifications, and each of these analyses exhibited only one significant dimension ($p < 0.0001$ for both the hypo and hyperthyroid classifications, Wilks'-Lambda test). For the hypothyroid status group, the BP component dataset was found to be most strongly influenced by the BMI > age > serum TSH level variables (all negatively correlated to the only significant canonical dimension), whereas for the hyperthyroid one, the dominating thyroid status variables were in the order age > serum TSH level > BMI (also all negatively contributing to the significant dimension). These results also at least partially reflect the significantly elevated mean BMI value of the hypothyroid status group over that of the hyperthyroid one.

Principal Component Analysis (PCA)

PCA analysis of a (simplified) dataset, which included only the BP components as predictor variables, and only thyroid status as a (qualitative) supplementary one, revealed at least some 'clusterings' of the these thyroid status classifications, the differences observed between the hyperthyroid and euthyroid groups being especially notable (Figure 4.6 shows a plot of principal component 2 (PC2) versus principal component 1 (PC1) for the varimax-rotated dataset). As noted for the RDA and CCA performed above, for this form of MV analysis, SBP, DBP and MAP values were significant contributors to PC1, whereas only the SBP:DBP ratio significantly contributed to PC2. PC1 and PC2 accounted for 67.91 and 31.92% of the total variance respectively (99.83% in total).

Figure 4.6 Principal component analysis



4.3. Discussion

Univariate statistical analyses revealed extremely highly significant 'between-thyroid status' differences ($p < 0.0001$) for the SBP, DBP, MAP, and uniquely the SBP:DBP ratio parameters. Moreover, BMI was significantly elevated in hypothyroid status patients over those of the healthy control and hyperthyroid status groups ($p < 0.0001$), and healthy controls had a significantly greater mean BMI value than that of hyperthyroid patients ($p < 0.0001$). χ^2 contingency table analysis revealed very strong associations between overweight status (BMI < or ≥ a threshold value of 23) and (1) euthyroid and hypothyroid disease status classifications ($p < 0.0001$) and (2) euthyroid and hyperthyroid classifications ($p < 0.018$). Partial correlation analysis demonstrated significant or highly significant correlations of (1) SBP, DBP and MAP BP components with blood serum TSH level for the hypothyroid group (all positive); DBP and MAP values with serum T4 concentration for the hyperthyroid group (also both positive); and intriguingly, SBP, DBP and MAP indices with serum T4 level (all positive), plus a negative one between SBP:DBP ratio and serum TSH concentrations for the euthyroid group. These results clearly indicate the importance and significance of systolic and/or diastolic hypertension in hypo and hyperthyroidism.

MV permutation tests performed via RDA demonstrated powerful associations between thyroid disease status and each of the BP components. Moreover, CCA of the complete (i.e. the combined hyperthyroid, hypothyroid and euthyroid status groups) revealed two highly significant dimensions between the BP component dataset and that comprising both

serum thyroid status biomarkers, age and BMI values, the first containing marked influences from SBP, DBP, MAP (response variables) and serum TSH concentration, BMI and age (explanatory variables), whereas the second contained highly significant contributions from SBP:DBP ratio (response variable) and serum T4 level (explanatory variable), i.e. the second dimension was ascribable to the hyperthyroid status classification, results consistent with those acquired from the above RDA conducted. PCA scores plots revealed at least some clustering of the three thyroid status classifications, and, as observed with CCA performed, the SBP, DBP and MAP values were found to be significant contributors to the first principal component, whereas only the SBP:DBP ratio significantly contributed to the second.

Although essential hypertension is more common, secondary hypertension is increasing and is now prevalent in view of associated disorders, which are more common in females (162). Furthermore, thyroid disorder is the most common endocrinological disorder, and hypertension is more often observed in thyroid diseases. However, to date there are only limited studies confirming this association (80). Isolated systolic hypertension is common in hyperthyroidism, and systo-diastolic hypertension (with an associated elevated DBP rather than SBP values) is prevalent amongst hypothyroid patients (80, 81). Hence, the SBP and SBP/DBP ratio components are expected to be greater in hyperthyroid subjects. Although both SBP and DBP values are elevated in hypothyroidism, the SBP/DBP ratio will be expected to be lower in patients with this condition, as observed here. Moreover, since the thyroid status-mediated increase in DBP is greater than that of SBP in hypothyroidism, MAP values are also expected to be higher in this class of patients.

4.3.1 Mechanisms of hypertension in hyperthyroidism

In hyperthyroidism, serum T3 and T4 levels are elevated, and its TSH concentration is diminished. T3, the active form of the thyroid hormone system, reduces systemic vascular resistance through dilatation of the arteriole and relaxation of vascular smooth muscle. Hyperthyroidism increases heart rate (HR), cardiac contractility and blood volume, and HR is a strong predictor of CO since it affects both systolic and diastolic function (60). In hyperthyroidism, HR may be elevated up to 40% of its basal value, and CO increases up to 300% when compared with that of hypothyroid patients (163). SVR largely regulates afterload which, in turn, depends on the arterial compliance and aortic impedance. Moreover, an increased capillary density and expression of vascular endothelial growth factors have been reported in thyroid diseases (164, 165).

Thyroid hormone-induced vascular muscle relaxation through an increased level of nitric oxide (NO) production from endothelial cells has been demonstrated in experimental models (165). T3 increases the synthesis of cardiac proteins associated with cardiac hypertrophy through the activation of myocyte-specific genes (9). Furthermore, the non-genomic effect of T3 includes its effect on membrane ion channels for sodium, potassium, and calcium, actin polymerisation, mitochondrial proteins and further intracellular cardiac signaling pathways (164). The above cardiogenic mechanisms explain the pathogenesis of hypertension in hyperthyroidism. However, anti-hypertensive treatment with ACE inhibitors in experimental models reduces BP, but not CO and HR (165, 166), suggesting the possibility that some other non-cardiogenic mechanisms contribute to hypertension in

thyroid disorders. Even in a hypertensive euthyroid population, thyroid hormones may be associated with left ventricular (LV) remodelling and mass, independent of LV and renal dysfunctions (167).

The juxtaglomerular apparatus of the kidney is sensitive to volume and BP. Since T3 decreases SVR and afterload, there will be a decrease in mean BP, which, in turn, activates the RAAS cascade and promotes an elevation in renin synthesis, blood volume and preload that contributes to CO value, which is raised in hyperthyroidism (168). An increased number of β-adrenergic receptors are found in the renal cortex of experimental models with hyperthyroidism, and β-adrenergic stimulation enhances renin secretion (166). Additionally, thyroid hormones influence baroreflex function and the autonomic nervous system, which are essential for the maintenance of both HR and BP, and hence both play a significant role in the development and progression of hypertension.

In view of the above hemodynamic effects, increases and decreases in the SBP and DBP components, respectively, will be expected, and consequently pulse pressure will be elevated. Pulse pressure serves as a marker of increased arterial stiffness, and also serves as a high index factor for cardiovascular risk, especially in the elderly population (169). In a previous study, a reduction in nocturnal BP was identified amongst hyperthyroid subjects with hypertension (170). An additional investigation involving a 24-hr. BP monitor demonstrated a similar mean value of this parameter in normotensive hyperthyroid patients when compared to that of normotensive euthyroid individuals (171). Treatment of

hyperthyroidism decreases pulse pressure, HR and CO, and subsequently BP. In a further report, hypertension was found to normalise to baseline normal range values following thyroidectomy for functional thyroid gland adenocarcinoma (172).

Sub-clinical hyperthyroidism (SHY) is characterised by normal serum T3 and T4 levels coupled with diminished TSH ones, and this condition is also common. However, predominantly, SHY never produces any clinical signs. Interestingly, Tamer *et.al.* noted an increased left ventricular (LV) mass and cardiac workload in SHY patients (173). However, to date there is no evidence available for hypertension in SHY patients, which has been confirmed by a community-based study (174).

4.3.2.Mechanisms of hypertension in hypothyroidism

Hypothyroidism is the second most common cause for secondary hypertension (following renal hypertension); however, it is often overlooked. The prevalence of hypertension amongst hypothyroid patients varies from 1 to 50% (175). Such a substantial variation in prevalence is ascribable to variable criteria in defining hypothyroid disease and hypertension, and also to differences in the age of subjects studied (176). As discussed above, thyroid hormones play a key role in the modulation of hemodynamic parameters. Hypothyroidism increases SVR and arterial stiffness in view of its vasoconstrictor effect on vascular smooth muscle (177), sympathetic nervous system stimulation, and decreases in β-adrenergic receptors (coupled with a parallel increase in α-adrenergic response) (178).

Hypothyroidism causes myxedema of the arterial wall which, in turn, gives rise to hypertension (177).

Hypothyroidism reduces renal blood flow and the glomerular filtration rate (GFR), with inappropriate ADH secretion (i.e., a mildly increased ADH). Consequently, there is free water retention with an associated increase in total body water, a decrease in intravascular volume and hyponatremia (179, 180). Sodium transport in vascular smooth muscle and the kidney is regulated by the lithium-sodium (Li^+-Na^+) counter transport mechanism; indeed, in essential hypertension, there is an increased Li^+-Na^+ counter transport (181). Thyroid hormones may also alter Li^+-Na^+ transport, which is more pronounced in hypothyroidism, and hence hypothyroidism may cause hypertension in this manner (182). In addition, hypothyroidism gives rise to low renin and angiotensin levels, which can cause salt-sensitive hypertension (183, 184). Hypothyroidism is frequently associated with metabolic syndrome and obesity (86, 185), which are also predisposing factors for hypertension. Elevated plasma TSH concentrations (probable hypothyroidism) in patients with metabolic syndrome independent of serum T3 and T4 biomarker values suggest it to be a component of the metabolic syndrome (186). Asvold *et. al(82)* found a linear increase in both systolic and diastolic BP components with increasing serum TSH levels in both men and women (i.e. significant positive correlations were observed).In a further study, mean day- and night-time DBP values were also found to increase linearly with TSH levels (187). Intriguingly, diastolic BP elevated significantly during changes from hyperthyroidism to hypothyroidism, and also normalised to normotensive values after the achievement of euthyroid status and low plasma renin levels in hypertensive hypothyroidism (188).

Sub-clinical hypothyroidism (SHO) is classified as a condition associated with high serum TSH, but normal serum T3 and T4 concentrations, with or without clinical symptoms; however, this condition has been associated with diastolic hypertension (174). Various studies have indicated an association of hypertension with SHO (84, 174, 189), whereas Duan *et. al.* (8) did not find any such association. Notwithstanding, Dagre *et. al.* (190) found a strong relationship between SHO and both systolic and diastolic classes of hypertension. Moreover, endothelial dysfunction is more prevalent in hypothyroid patients (191), and pregnant women with sub-clinical hypothyroidism have an increased risk for severe pre-eclampsia when compared with euthyroid subjects (192).

In one study (44), an elevated serum TSH concentration was noted in families with a high prevalence of hypertension, which suggests the possibility of genetic polymorphism of this biomarker with type-2 iodothyroninedeiodinase genes which are involved in the modulation of BP regulation and serum levels of this biomarker. In hypothyroid patients, treatment with T4 reduces arterial stiffness, vascular resistance and BP (190). Hence, early diagnosis and management are required in such patients in order to reduce cardiovascular risk status.

4.3.3 Treatment of hypertension in thyroid disorders

In thyroid disorders, hypertension is reversible once thyroid function attains normalisation status, although this may not necessarily occur shortly thereafter. However, treatment with antihypertensive drugs is mandatory in the case of moderate to severe hypertension.

Isolated systolic hypertension represents the strongest risk factor for cardiovascular disease, which is common in hyperthyroidism (80). β-adrenergic blockers are preferred in such cases, since they not only reduce BP, but also alleviate further symptoms of hyperthyroidism such as tremor, tachycardia and anxiety (193). Propranolol inhibits the peripheral conversion of T4 to T3, a more active form of these thyroid hormones. Individuals with relative contra-indications for β-adrenergic blockers may tolerate β1-selective drugs more effectively. Calcium channel blockers (CCBs) may be considered if patients are unable tolerate β-blockers, and felodipine has been shown to reduce BP and SVR in hypertensive hypothyroid patients who did not respond to hormone replacement (194). ACE inhibitors offer a potential benefit to hypertensives with thyroid disorders, since they reduce intraglomerular pressure (168). In most cases, hypertension associated with hypothyroidism is salt-sensitive, although in hyperthyroidism it is salt-resistant. Hence, a typical salt-sensitive and low renin form of hypertension is frequent in hypothryroidism, and this is more effectively treated with a low sodium diet, CCBs and a diuretic.

4.3.4. Effect of treatment of thyroid disorders on blood pressure

In a study conducted by Dernellis *et. al.*, hypothyroidism was associated with hypertension and aortic stiffness. Amongst the patients who received thyroid replacement therapy, 50% of them showed reversibility in their hypertension and aortic stiffness was decreased among all patients. After the achievement of euthyroid state in hyperthyroid patients who received treatment, atrial fibrillation reverted to sinus rhythm in the majority of patients

(195). In a cohort study conducted by Razvi *et. al.*, thyroid replacement therapy is found to be beneficial in patients with SHO in the terms of cardiovascular events and mortality (196). It is noted that ventricular function improves with thyroid replacement therapy even in SHO (196). In the settings of ischemic heart disease, treatment of hypothyroidism proven to offer clinical benefits such as reduction of blood pressure, afterload and cardiac output and there by decrease the oxygen demand ischemia (176).

4.3.5. Need for TSH testing

The International classification of diseases ninth edition (ICD – 9) recommends screening TSH testing for the following diagnosis as listed in the table 4.3 (61).

Table 4.3. Common diagnosis with ICD – 9 codes recommends TSH testing

Diagnosis	ICD-9 Code
Anemia	285.9
Atrial fibrillation	427.31
Hypertension	401.0
Hypercholesterolemia	272.0
Mixed hyperlipidemia	272.4
Diabetes mellitus	250.00
Obesity	278.00
Weight gain	783.1
Weight loss	783.21
Myopathy	359.9

ICD-9 indicates *International Classification of Diseases, Ninth Edition.*

4.4. Conclusions

Isolated systolic hypertension and an increased pulse pressure are more common in hyperthyroidism, whereas combined systo-diastolic hypertension (in which elevations in DBP exceed those in SBP) is more pronounced in hypothyroidism. We have also noted significant associations between SBP:DBP ratios, MAP values, and thyroid disease status. Indeed, employment of the SBP:DBP ratio may serve as a valuable diagnostic index for monitoring the development of hypertension and its response to treatment in hyperthyroid patients. Therefore, practitioners may be motivated to record BP in thyroid disorders and provide appropriate medications in order to reduce cardiovascular mortality/morbidity risks. The use of 24 hr. ambulatory BP measurements will not only facilitate this diagnosis, but also provide valuable information regarding load, circadian variation and BP variability, which are all considered as important risk factors and surrogate markers for cerebro and cardiovascular events.

4.5. Limitations

The limitations of this investigation are that correlations of the dataset acquired with duration of illness were not explored. 24 hr. ABP was not utilised and there was not a follow-up of BP in these patients subsequent to the initiation of specific thyroid disease treatment(s), and the non-estimation of serum T3 levels (each of these are ascribable to resource limitations). Hence, a larger clinical trial with a long-term follow-up period is warranted.

CHAPTER 5: KNOWLEDGE, ATTITUDE, BEHAVIOUR AND PRACTICE (KABP) OF HYPERTENSION MANAGEMENT AMONG PHYSICIANS

5.1 Methodology

A structured questionnaire was distributed amongst the 117 physicians practicing in urban parts of India and of these, 104 physicians responded. However, amongst the 104 questionnaires returned by physicians, four questionnaires were not properly completed (less than 15% of the questions were answered), and hence only 100 questionnaires with answers were considered. The response rate was 85%. Name, age and gender of the physicians were provided as optional questions in order to achieve a satisfactory response rate. However, the questionnaire was distributed amongst physicians aged between 30-40, and all physicians were required to have managed hypertensive cases for a minimum of 5 and a maximum of 10 years.

5.2 Results

All physicians treated both old and new hypertensive cases in their practice, and Tables 5.1 and 5.2 provide the mean number of cases per month seen by them.

Table.5.1 Number of New Hypertensive cases seen by Physicians

Number of Physicians	Approximate number of new cases per month*
55	15
26	25
19	30

Legend: * approximately

Table.5.2. Number of older hypertensive cases seen by physicians

Number of Physicians	Old cases per month*
36	50
27	60
47	70

Legend: *approximately

We have considered JNC 7 criteria for hypertension, and all cases were categorised accordingly.

Table 5.3 Distribution of Hypertensive cases seen by Physicians (Hypertension according to JNC 7 criteria)

No.	Category	Percentage
1	Pre HTN	30 – 35
2	Stage – I	30 – 35
3	Stage – II	30 – 40

Legend: JNC 7 - Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (197)

10% of physicians have seen and reviewed few cases of hypertensive emergency and urgency, and unfortunately 3 patients were aged less than 30 years. More than 75% of physicians do not routinely check the blood pressure of individuals visiting the clinic for one or other clinical problems. Furthermore, the time spent by physicians whilst evaluating their patients is an important factor for the clinical outcome in disease management. Table 5.4 provides this information for hypertensive cases.

Table 5.4 Time spent with hypertensive cases by physicians

Time in minutes	First visit	Therapy titration	Revisit
Less than 5	----	10	39
5 – 9	57	43	49
10 – 14	24	47	22
15 and more	19	--	--
Total number of physicians	100	100	100

As noted, the majority of the physicians spent less than 10 minutes during appointments with their patients. None of the physicians responding were reviewed via the guidelines available for the management of hypertensive patients. Physicians reported that approximately 15 to 20% of their patients were only on diet control for hypertension, and about 25% of them had one or other end organ damage. None of the physicians referred their patients with resistant hypertension for a specialist opinion (198). Most physicians start their patients on monotherapy for new hypertensive cases (Table 5.5), and their choices of preferred drug vary as listed in Table 5.6. Table 5.7 indicates the preferred drugs of choice by physicians for switching to/or adding other drugs for one or further reasons such as inadequate control of blood pressure, resistant hypertension, failure of monotherapy, and the occurrence of side-effects.

Table 5.5 Patients receiving monotherapy under responding physician care

Percentage on Monotherapy	Physicians' response
Less than 15	52
15 – 24	48
Total	100

Table 5.6. Preferred first drug of choice for uncomplicated hypertension by physicians, if already on monotherapy

Name of the drug	Number of Physicians
Diuretics	49
Calcium channel blockers	36
Beta blockers	15

Table 5.7. Preferred drug of choice by physician without end organ damage/co-existing illness for switching to/adding other drugs for one or other reasons as mentioned in the text

Anti-hypertensive agents	Number of Physicians*
ACE inhibitors	35
ARBs	67
Beta blockers	39
Calcium channel blockers	76
Loop diuretics	19
Thiazide	49
Aldosterone antagonist	13
Alpha blockers	22
Vasodilators	19

Legend: *Number overlapping with each other, ARB – angiotensin receptor blocker, ACE inhibitors – angiotensin converting enzyme inhibitors

For monotherapy, most physicians prefer diuretics and calcium channel blockers for hypertension regardless of the age group. For combination therapies or switching over to other drugs, calcium channel blockers and ARBs are most commonly prescribed. Physicians reported that an average of 10 to 15% of their patients discontinued treatment by themselves. In about 15 to 25% of the patients, physicians switched the drug therapy. There are number of reasons for this occurrence which are listed in Table 5.8.

Table 5.8. Reasons for switch-over of the anti-hypertensive drugs prescribed by physicians

Reasons	Number of physicians*
Inadequate BP control	49
Side effects	58
Availability of newer / better compounds	56
Interaction with other drugs	09
Cost of medicine	12
Non availability in market	05

Legend: *Number overlapping with each other; BP – blood pressure

Inadequate blood pressure control, side-effects and the availability of newer therapeutic compounds are the most common influencing reasons for physicians choice to switch over to other drugs. Also, from clinical practice, side-effects ascribable to the drugs administered are the most important and common complaint amongst patients, which may lead to poor compliance and hence inadequate disease control. Therefore, it is very important for healthcare professionals to enquire about the adverse/side-effects of the treatment. From the physicians viewpoint, the adverse/side-effects observed for each class of drug are listed in Table5.9.

Table 5.9. Adverse/side-effects for each major class

Anti hypertensive agents	Percentage developed side effects
ACE inhibitors	35
ARBs	5
Beta blockers	10
Calcium channel blockers	5
Loop diuretics	12
Thiazide	10
Aldosterone antagonist	5
Alpha blockers	5
Vasodilators	5

Legend: ARB – angiotensin receptor blocker; ACE – angiotensin converting enzyme

From our observations from physicians, it should be noted that ACE inhibitors cause side-effects in the majority of the patients. Hence, most physicians prefer ARBs rather than ACE inhibitors for combined therapy/switching over to other drugs, without even attempting to employ ACE inhibitors (Table 5.7). The most common side-effect observed with ACE inhibitors is dry cough, and Table 5.10 indicates the most common side-effects observed with anti-hypertensive drugs.

Table 5.10. Prominent adverse effects observed with anti-hypertensive drugs by responding physicians

Adverse effects	Physicians reported*
Dry cough	37
Wheezing	24
Oedema legs	13
Palpitation	24
Giddiness	17
Gynaecomastia	2
Weakness	24
Muscle cramps	12
Constipation	04

Legend: *Number overlapping with each other

There are multiple ways to manage these side-effects which all depend on clinical circumstances such as seriousness of the side-effect, clinical condition, the patient's tolerability, understanding and awareness. In most clinical scenarios, physicians prefer switching over to other drugs in view of the availability of other classes of drug, an inability to counsel/convince the patient, and/or for better compliance. The responding physicians' choices in such instances are provided in Table 5.11.

Table.5.11. Physician's choice when side-effects are noticed with particular anti-hypertensive drugs

Choice	Physicians reported*
Dose reduction	39
Switching over	75
Investigations	13
Addition of another drug	07
Convince the patient	05
To analyse the interactions	01

Legend: *Number overlapping with each other;

As a commonly-encountered action, most physicians prefer switching to other drugs rather than advising a dose reduction. Also, most of them do not attempt to counsel their patients and investigate the reasons for side-effects such as drug interactions or co-existing illnesses. In the survey, 39% of physicians tried to reduce the drug dose as one of the measures. Although it is considered as an improved option, it carries the risk of inadequate blood pressure control. Table 5.12 indicates the preferred drug choices made by physicians when patients experience such side-effects.

Table 5.12. Preferred drug by Physicians when patient had adverse effects

Class of drugs	Physicians reported*
ARBs	37
Calcium channel blockers	23
Alpha blockers	12

Legend: *Number overlapping with each other; ARB – angiotensin receptor blocker

Overall, awareness regarding hypertension and its treatment amongst the general public is still far from a satisfactory level of acceptance. Hence, we requested information from the responding physicians concerning the reasons for poor compliance, and also barriers for disease management.

Table.5.13. Reasons for poor compliance, (numbers reported /100) and barriers for physicians in the management of hypertension

Reasons	Physicians reported *
BP Controlled	17
Forgotten to buy	25
No symptoms	17
No belief in medicines	09
No support from family	16
Non supply of medicines	24
Want of money	12
Religious as reasons	09
Travel	15
Missed tablets	24
Bed effects of drug	21
Cost of medicines	34
Switch over to other system of medicines	14
Neighbour's influences	04
Punish family members	12
Missed prescription	07
Multiple drugs	10
Lack of awareness among patients	100

Legend: *Number overlapping with each other.

There are many possible reasons for the poor compliance as listed in the Table 5.13. However, the main factor is lack of awareness amongst patients and the general public regarding control, treatment and the complications of hypertension. Of course, this can be

achieved through physician-patient interaction, patient education and motivation. There are few recommendations suggested by the responding physicians for the improvement of patient treatment compliance (Table 5.14). It is therefore very important that physicians should provide details regarding the complications of hypertension through physician-patient interactions, since many patients are unaware of the complications of hypertension (Table 5.15).

Table.5.14. Suggestions to improve compliance

Suggestions	Physicians responding*
Physician-patient interaction	90
Patient-to-patient interaction	37
Interaction with care givers	45
Patient education	65
Dosage simplification	76
Singe tablet / day	44

Legend: *Number overlapping with each other

Table.5.15. Frequency of end organ damage amongst patients of the responding physicians

End organ damage	Frequency (%)*
Coronary artery diseases	25 to 45
Stroke	15 to 25
Chronic kidney failure	12 to 20
Eye – Retinopathy	40 to 60

Legend: *approximate

Although pharmacotherapy remains the standard treatment for hypertension, diet and lifestyle modifications remain an essential need for hypertensive patients. Many patients on pharmacotherapy may not have adequate control of blood pressure if weight reductions and diet modifications (especially salt reduction) have not been considered. These are common issues in such patients (Table 5.16).

Table.5.16. Common issues in the management of hypertensive patient

Issues	Physicians responding*	Number of Physicians referring their patients for particular measure*
Diet counselling	84	0
Weight reduction	69	21
Salt restriction	100	41
Regular medication	100	78
Life style changes	100	9

Legend: *Number overlapping with each other

In this study, only 15% of physicians conducted a hypertension awareness or counseling programme, and unfortunately less than 15% of patient population attended awareness or counseling sessions. None of the physicians referred their patients to a dietician, even for

patients who were overweight or had obesity problems, together with resistant hypertension. Only 14% of the physicians standardised the sphygmomanometer or checked the blood pressure apparatus for errors, and 42% of the physicians are familiar with the zero error term in sphygmomanometer use. None of the physicians were aware of the exact size of blood pressure cuff (Table 5.17); an inappropriate cuff size significantly influences blood pressure readings.

Table.5.17. Physician's knowledge of blood pressure cuff size

Blood pressure cuff for	Physician answer	
	Yes	No
Infants	--	100
Paediatrics	---	100
Normal adult	---	100
Overweight/obese	---	100
Formulae to calculate cuff size	---	100

In the questionnaire, we have provided a column for open-ended suggestions for physicians to mention any other information related to hypertension and its management. Table 5.18 illustrates general information related to hypertension provided by the responders.

Table.5.18. Further information related to hypertension provided by responding physicians

Response status	Physicians responding*
Hypertension is increasing	67
Requirements for community education	85
Hypertension emergencies increasing	29
Bad life styles	27
Provide free treatment at all places	17
Requirement for hypertension guidelines	100
Challenges for hypertension management	23

Legend: *Number overlap each other

Among responders, only 7% of the physicians had attended previous training or seminars in hypertension. Most of the physicians are interested in attending seminars in hypertension management. Moreover, approximately 80% of the physicians are not well aware of the hypertension management guidelines. Therefore, we have assessed the physicians needs and demands in the particular aspects of hypertension, and these are tabulated in Table 5.19. I have scored this requirement from 0 to 100 %, with 0 being the least and 100% the most important. I have also requested that physicians write their needs in different areas of learning in hypertension as noted in the Table 5.19 (first column – areas of interest/learning).

Table.5.19. Physician's attitude or requirements regarding the learning aspects of HTN

Areas of learning/ interest	0 %	10 %	20 %	30 %	40 %	50 %	60 %	70 %	80 %	90 %	100 %
1.Historical aspects	0	95	0	0	0	0	0	0	0	0	5
2.Epidemiology	0	95	0	0	0	0	0	0	0	0	5
3.Symptoms	0	0	10	3	0	0	0	0	0	0	87
4.Signs	0	0	9	4	0	0	0	0	0	0	87
5.Clinical evaluation	0	0	5	5	0	0	0	0	0	0	90
6.Investigation	0	0	0	0	0	0	0	0	0	0	100
7.Assessment	0	0	0	0	0	0	0	0	0	0	100
8.Drugs used in practice and future	0	0	0	0	0	0	0	0	0	0	100
9.Adverse effects of drugs	0	0	0	0	0	0	0	0	0	0	100
10. Course and complications	0	0	0	0	0	0	0	0	0	0	100
11.Audit – how to check records	0	15	12	11	5	9	14	17	10	5	2
12. Issues in pregnancy & lactation	0	0	0	0	0	0	0	0	0	0	100
13. Follow up	0	0	0	0	0	0	0	0	0	0	100
14. Prevention	0	0	0	0	0	0	0	0	0	0	100
15. Traditional practices used	0	25	0	0	0	0	0	0	17	0	58
16. Alternative medicines	0	17	0	0	43	0	0	21	0	0	19
17.Socioeconomic aspects	0	13	0	0	0	0	0	0	60	17	10
18. Yoga / meditation	0	0	0	0	1	0	9	0	0	0	90
19. Legal issues	0	0	0	0	0	0	0	0	0	4	96
20. Patient education	0	0	0	0	0	0	0	24	10	21	45
21. Formulation of standard guidelines for hypertension	0	0	0	0	0	0	0	0	0	0	100

Legend: % - percentage; HTN – hypertension, in the above table, the percentage indicates the priority/rank, with 0% as least important, and 100% as most important. The numbers given inside indicates the number of physicians responding.

From the above Table, it should be noted that most physicians require training in the management and preventative aspects of hypertension. Indeed, all physicians mandate the need for standard local guidelines for hypertension. The majority of the responders are not interested in audit; however, audit represents an essential component of clinical governance which provides an insight into the errors made, and also suggestions to improve the standard of care.

5.3. Discussion

Early and prompt diagnosis of the hypertension is mandatory in view of the asymptomatic nature of the disease, and also potential complications arising if left untreated. From the above observations, we conclude that KABP towards blood pressure management amongst the physicians was sub-optimal, a similar observation to that made in our previous observations amongst interns, together with those from a series of additional previous studies(21, 198-202).

The United States Preventive Services Task Force (USPSTF) advises physicians to screen individuals aged 18 and above for hypertension. Indeed, there are many factors associated with the patients which lead to poor compliance and most importantly, as suggested by all physicians, was a lack of awareness about hypertension amongst the patients themselves (199). Physicians play a key role in educating patients about the disease; however, in this

study, less than 15% of patients conducted such an awareness programme (199). Moreover, most of the patients are not interested in attending such an awareness programme. Furthermore, another important issue is that regarding self-medication amongst the patients. Hence, clinicians need to stress the importance of medications and their associated side-effects.

The cost and affordability of the medications prescribed influence the compliance of patients. Indeed, there are many barriers for the physicians involved concerning for the management of hypertension, and these are discussed in the results section and its associated tables. The leading factors are lack of awareness regarding the disease and its development, and also financial implications as previously noted by Wang (203). The physician's approach towards the non-pharmacological management of hypertension, such as lifestyle modification, dietary advice and weight reduction, needs to be strengthened. Unfortunately, most of the patients prefer a non-pharmacological approach, which is currently unavailable (203). Furthermore, a lack of knowledge of hypertension guidelines amongst physicians remains as a further barrier for the management of this condition (204).

Drugs such as diuretics and beta blockers are recommended as the first-line drugs in uncomplicated hypertension (197). ACE inhibitors and calcium channel blockers are useful in managing hypertension with associated co-morbidities such as chronic kidney disease, angina, etc. (197), or for combination therapies. Moreover, ACE inhibitors and calcium channel blockers are more expensive than diuretics, and thiazide diuretics are effective in uncomplicated hypertension cases(205, 206). However, the use of drugs of

choice for hypertension varies from country to country, and also depends on the physician's specialty (207). In addition, there are variations in the clinical practice amongst physicians for managing hypertension within the country, even for regions with standard guidelines available (208). In this study, all physicians are internist. However, Mosca *et. al*., demonstrated variations in the pharmacological management of hypertension between primary care physicians, obstetricians and cardiologists (207). Most of the cardiologists preferred to prescribe ACE inhibitors, beta- blockers and calcium channel blockers, since these drugs have proven benefit in cardiovascular health (207). Moreover, cardiologists urged the importance of lifestyle modifications, and also encouraged the patients for self-medications more so than other specialists (207), and most cardiologists are aware of recommendations made by hypertension management guidelines(203).

Italian primary care physicians prefer ACE inhibitors and calcium channel blockers; however, diuretics and beta-blockers are preferred more in England. These variations are ascribable to variations in practice and guidelines available worldwide (201). In Ireland, despite good access to ambulatory blood pressure monitor (ABPM), an invaluable clinical tool, the use of ABPM in hypertension management is not encouraged because of lack of time, cost and remuneration as noted by General Practitioners (GP) (209). A survey conducted amongst general practitioners in Sweden showed that GPs accept higher blood pressure levels than those recommended in their guidelines, and elderly patient populations appears to serve as a barrier to them, preventing their initiation of drug therapy (210). A low prevalence rate of hypertension amongst the Saudi Arabian population has prompted physicians to adhere to local clinical guidelines for hypertension management (211). Few

physicians measured blood pressure appropriately, and the correct diagnosis of hypertension was not established in many patients. Moreover, regular checks of blood pressure performed in all clinic patients have not been encountered. Additionally, one or more items such as clinical examination, investigations and the prescription of optimal drugs of choice have been missed in many patients (211). Eastman noted that hypertension is the most common problem in Australia; however, it remains untreated in view of a lack of clarity and consistency in the evidence-based guidelines available for hypertension management (212). A large number of patients had never checked their blood pressure within last 12 months preceding the survey, although they had the opportunity to visit physicians (213). Patients and physicians prefer medications with the fewest side-effects for reasons of better compliance (201). Unfortunately, physicians lack the knowledge made available by specific guidelines (214). More appropriate use of the drugs which consider all possible clinical aspects (including clinical situations and affordability to the patients) is mandatory since this predicts the effective compliance of the patients (200).

Most of the patients diagnosed with hypertension received pharmacotherapy (201). In our observations, physicians mentioned that most of their patients required a switch in drug therapy in view of one or more of the reasons noted above (215); however, in further reports, only a limited number of patients were required to switch drug therapies (201, 216). The major reason for this switch is inadequate control of blood pressure as observed in this study (217). It is therefore very important for the physicians to monitor the response and side-effects of the drugs in patients who are all on pharmacotherapy. Ambrosioni et. al. documented that physicians reported that about 10 to 20% of their patients had side-effects

with medications, although 69% of them reported such side-effects arising from the use of these drugs. Furthermore, physicians are not aiming to achieve the target blood pressure in their patients (198). This huge variation may be attributable to a lack of close observation of symptoms. As with previous studies performed, even in our study physicians failed to spend sufficient time with patients in their first and subsequent visits (198, 201). Many physicians emphasised the importance of patient education and awareness. However, short clinical encounters with patients renders it much more difficult for physicians to educate the patient during their visit (198). Thus, the lack of a physician's instructions to the patients regarding disease management and their associated complications and administered drug side-effects lead to poor patient compliance, a phenomenon which gives rise to the many complications noted (of a reversible or irreversible nature).

5.3.1.Demands for Physicians in hypertension management learning

Most of the physicians are required to attend appropriate training courses or seminars for hypertension management (202). Further exploration of the learning aspects of hypertension revealed that many of them are interested in learning the clinical management and prevention of hypertension rather than the historical aspects and epidemiology. Also, many of them did not focus on clinical audit (which represents an essential part of clinical governance) in order to promote and maintain the standard of care.

In a previous study, it has been demonstrated that physicians working in academic centres with elements of teaching and assessment, and also dedicated settings for hypertension control and management have higher performance rates than physicians in general or the

private health care centres (202). This indicates the major requirement for continuing education for disease management to produce an improved standard of care. As observed in this study, physicians clearly underestimate the challenges of hypertension management (218).

Cuspidi et. al. conducted a study which explored primary care physicians' approach towards hypertension management (219). Interestingly, they made two new observations: (i) physician's age and duration of the practice inversely related to the knowledge of guidelines, and (ii) an adequate blood pressure control achieved by many doctors probably reflected their own skills, and is inversely related to guideline knowledge (219). This urges the importance of intensive professional education and training through continuing medical education, and particularly for physicians with a longer duration of practice (219). A similar observation, along with diminished knowledge guidelines amongst rural physicians was noted amongst Polish primary care physicians (204). Therefore, the investigator hypothesize a fact from the above observations, specifically that the greater the age and longer the duration of practice of physicians, the busier they are with their clinical practice. Hence, they may have little or no time to read and review the latest guidelines, or to attend any seminars. Also, access for rural physicians to attend relevant training programmes or to access materials is complicated (204).

5.3.2.Medical Education and Training

As noted previously, KABP amongst interns was sub-optimal, an observation which was consistent with studies from developed and developing nations (21, 90-92). A study

conducted in Jordan revealed that junior doctors (who were recent graduates) lack the clarity in hypertension management which was characteristic of their seniors(220). This is probably ascribable to a lack of training in these aspects during medical education (90). In addition, the above observations strongly emphasise the requirements for continuous update in medical curricula for medical students, and medical schools should include programmes on the quality control of medical devices (blood pressure apparatus) and the management of hypertension (21).

5.3.3.Requirement for local guidelines

There is urgent requirement for local guidelines in managing hypertension (221). Indeed, guidelines need to focus on the clinical, social and economical aspects of patients. Moreover, it should focus on ease of access, availability and administration (221). Hence, the Ministry of Health should implement nationally agreed guidelines by taking all aspects into consideration for the better control of disease and compliance.

5.4.Conclusion

Overall, KABP towards hypertension guidelines and management amongst physicians was found to be sub-optimal. There are many barriers for physicians to treat their patients for improvements in health care. All physicians should be encouraged to monitor blood pressure as a routine check for all of their patients, a development which will help us diagnose the disease earlier.

The Ministry of health or national societies should emphasise the need for training, and also promote training through continuing medical education. There is also a major requirement for local guidelines for the treatment and management of hypertension. However, guidelines should be designed according to clinical as well as socio-economic aspects of the patients and should be cost-effective. Moreover, all doctors at primary care level should be educated regarding hypertension management. Promotion of evidence-based medicine and curriculum is mandatory in order to bridge the gap in knowledge of the physicians involved in the management of such chronic diseases.

5.5. Limitations of the study

A relatively small dataset was employed, physicians from same region were selected (urban and the same Indian city), and the same specialty was involved: these represent the limitations. Further studies with a larger dataset focused on comparing the knowledge acquired amongst physicians of differing specialties and locations (i.e., urban *versus* rural) are warranted.

CHAPTER 6. AWARENESS OF HYPERTENSION AMONGST THE GENERAL PUBLIC

6.1. Methodology

A Questionnaire survey was conducted amongst 100 hypertensive patients after briefing the participants on its completion. The questionnaire was provided to the patients in their local language (Tamil), since they did not understand English. The response rate was 100%, and there were 54 males and 46 females in our study group; 30 patients were from urban areas and the remainder were from rural areas. The patients' educational status was categorized according to the modified Kuppuswamy's scale (222). All of the patients recruited to the study group were diagnosed with hypertension for at least 5 and a maximum of 39 months.

6.2. Results

The age group of our patients varied from 35 to 64 with (mean age 46.5 years). Their demographic, educational status and domicile are provided in Tables 6.1 and 6.2. In our study group, *ca.* two-thirds of the patients were literates and from rural areas.

Table 6.1. Demographic pattern of the survey patient participants

Gender and Age Group			
Age in years	Male	Female	Total
35 – 44	18	15	33
45 – 54	24	22	46
55 – 64	12	09	21
Total	54	46	100

Table 6.2. Educational status and residence location of the patient participants

Educational status				Domicile			
Literate		Illiterate		Urban		Rural	
Male	Female	Male	Female	Male	Female	Male	Female
48	28	06	18	12	18	42	28
76		24		30		70	
100				100			

I have included only hypertensive patients. Also, all of these were diagnosed with hypertension for at least 5 and a maximum of 39 months. I have also provided the number of patients with their duration of hypertension treatment in Table 6.3.

Table 6.3. Duration of hypertension treatment for the patient participants

Duration of medication for hypertension			
Duration in months	Male	Female	Total
5 – 9	13	05	18
10 – 19	10	11	21
20 – 29	17	19	36
30 – 39	14	11	25
40 and above	0	0	0
	54	46	100

All the patients were requested to mention the name of prescribed medicines in the form.

Also, I have tabulated the answers and their association with educational status (Table 6.4).

Table 6.4. Patients awareness of the name of prescribed medicines

Number of patients aware of the names of prescribed medicines			
Yes		No	
Literate	Illiterate	Literate	Illiterate
37	08	39	16
45		55	

From the above table, it is clear that more than 50% of the patients did not remember the names of medicines that they were prescribed. On further analysis, 52% (39 out of 76) literates and 66% illiterates (16 out of 24) were unaware of their medication's names. This indicates that awareness status is sub-optimal amongst our patients, regardless of their educational status. Amongst 100 patients, clinicians checked the blood pressure in 92 patients, and nurses checked these parameters for the remainder. In India, doctors usually check the blood pressure since the sphygmomanometer is still in frequent use. The use of an automatic blood pressure monitor in India is not frequently encountered. None of the patients had blood a personal blood pressure monitoring device at home, and none of them were aware of usage of such devices. Table 6.5 demonstrates the participants' time of recent blood pressure checks.

Table 6.5. Recent (last) blood pressure check by the patients

Recent Blood pressure check			
Duration in months	Male	Female	Total
Less than 3	24	17	31
3 – 5	04	13	17
5 – 8	17	09	26
More than 8	09	07	26
Total	54	46	100

About 1/3rd of the patients had their blood pressure checked within the last 3 months. This status may not be appropriate, since some patients who may check their blood pressure routinely did not get their blood pressure check performed recently in view of one or more personal issues such as socio-economic problems, clinic visits and time factors. In order to acquire appropriate data, we have requested that our patients provide information regarding how often they have their blood pressure checked in the questionnaire. The majority of the patients did not answer that question and hence we were not able to provide data for it.

Table 6.6. Status of disease control in patient participants

Status of blood pressure control			
Under control		Not under control	
Male	Female	Male	Female
36	27	18	19
63		37	
100			

From the above Table, it should be noted that only 63% of patients had their blood pressure under control with medicines, whilst the remainder of them did not have adequate blood pressure control. Indeed, many of them discontinued treatments for hypertension. Only 12 patients (8 males and 4 females) amongst 100 patients had good compliance with treatment

for hypertension. There are multiple reasons listed by them for the discontinuation of treatment (tabulated in the Table 6.7).

Table 6.7. Reasons for discontinuing treatment(s) for hypertension

Reasons for discontinuing the treatment for hypertension			
Reasons	Number of males*	Number of females*	Total*
Blood pressure controlled	07	03	10
Forgotten to buy	02	06	08
No symptoms	01	13	14
No belief in blood pressure reading	05	03	08
No support from family	09	07	16
No medicine in the hospital	07	04	11
Due to financial constraints	09	01	10
Multiple reasons (2 or more reasons from the above)	06	05	11
Less information from physician	36	30	66
Less physician – patient interaction	40	38	78
No or low confidence in the hypertension treatment or physicians	25	28	53

Legend: *numbers overlapping each other

Although there are multiple reasons for this, including the socio-economic issues listed, the most common problems are poor physician-patient interactions, inadequate information

regarding the disease and its management from physicians, and a generalized lack of confidence either with treatment or physicians. This problem exists not only in India, but elsewhere. Hence, patient counselling/education and an enhanced level of physician-patient interactions are vital measures required in order to overcome such issues. Interestingly, many patients tried to obtain information regarding hypertension from other sources (as listed in the Table 6.8).

Table 6.8. Information obtained by patients participants regarding hypertension

Information about hypertension			
Information obtained through	Male*	Female*	Total*
Pictures/posters	12	03	15
Television	29	17	46
Radio	11	04	15
Books	03	01	04
Newspaper	14	02	16
Advertisement	09	01	10
Doctors and nurses	50	37	87
None (never obtained information from anything)	04	09	13

Legend: *number overlap each other

Healthcare professionals serve as the major narrators regarding health and disease. Indeed, although most of our patients obtained information through them, still lacking was information concerning adequate disease control. Therefore, the information obtained was probably of a superficial nature. Additionally, media is the most important messenger for delivering information about health and disease. Hence, there is a need to monitor, regulate and standardise the information delivered via this route. Many patients in our study group were aware of the non-pharmacological methods for hypertension control, and some of them have been adapted to control blood pressure. Tables 6.9 and 6.10 list the non-pharmacological approaches adapted by patients for hypertension.

Table 6.9. Non-pharmacological methods adopted by patients for hypertension control and monitoring

Methods adapted to reduce/control blood pressure			
Methods adapted	Male*	Female*	Total*
Weight reduction	21	14	35
Salt reduction	37	18	55
Diet reduction/change	17	19	36
Smoking cessation	19	00	19
Stop alcohol drinking	22	00	22
Physical activities/exercise	19	11	30
Regular blood pressure check-up and medication adjustment/titration	39	28	67
A combination of these	47	34	81

Legend: *number overlap each other

Table 6.10. Awareness amongst the patient participants regarding diet and lifestyle modifications available for the control of hypertension

Awareness amongst the public regarding diet/lifestyle modifications for hypertension			
Diet or lifestyle	Male*	Female*	Total*
Food with low salt	02	00	02
Food with high salt	34	12	46
Food with excess fat	24	11	35
High fibre diet	09	04	13
Eating green vegetables and green	36	13	49
Excessive water intake	17	09	26
Stop non-vegetarian food	27	14	41
No idea	05	03	08

Legend: *numbers overlap with each other

In India, alternative medicine is one of the common medical practices for the management of many diseases, including hypertension. Iindeed, alternative medicine is emerging throughout the world. There are some lifestyle modifications along with alternative therapy/methods practiced for hypertension management. The alternative methods adopted by our study patients for hypertension management are listed in Table 6.11.

Table 6.11. Alternative methods to reduce blood pressure in hypertension adopted by patient participants

Alternative ways to reduce blood pressure			
Methods adapted	Male*	Female*	Total*
Peace of mind	17	04	21
Avoid anger	36	21	57
Avoid stress	25	19	44
Yoga practice	17	04	21
Meditation	09	03	12
Eating fish	04	01	05
Prayers	26	27	53
Talking loudly	19	11	30
Avoid lifting heavy materials	15	09	24
No idea	04	03	07

Legend: *number overlap each other

Complications of hypertension include micro- and macrovascular damage. Unfortunately, the majority of the patients recruited to the study were not aware of the all the serious complications associated with hypertension.

Table 6.12. Patients' awareness of complications arising from hypertension

Awareness of complications of hypertension			
Complications	Male*	Female*	Total*
Myocardial infarction	23	12	35
Stroke	24	13	37
Bleeding in the brain	14	02	16
Renal failure	11	03	14
Damage to blood vessels	09	01	10
Heart failure	13	04	17
Not known	04	09	13

Legend: *number overlap each other

There are some views regarding hypertension amongst the general public which include that it is (1) a disease of the rich, (2) a preventable disease, together with many others as listed in the Table 6.13. Some of them have mentioned alternative medicine as the best treatment option for hypertension. Such views are obtained through old local language literatures, social conversations, their own personal or family or friends experiences, and sometimes through the media.

Table 6.13. Opinions on hypertension

Public opinion on hypertension			
Opinion	Male*	Female*	Total*
Disease of rich	17	14	31
Preventable disease	09	04	13
Long-term treatment	19	13	32
Alternative medicine is the best	13	04	17
Familial	12	04	16
Serious disease	07	01	08
No comments	22	19	41

Legend: *number overlap each other

6.3. Discussion

In India, the prevalence of hypertension is high (Figure 1.1) and there is a concern for further rapid escalations in the prevalence of this condition with regard to economic development, industrialisation, globalisation and diet/lifestyle changes amongst the population (223). However, the awareness, treatment and control of hypertension amongst the general public are extremely low as observed in this study, which has been demonstrated previously (100). Furthermore, there is also a substantial disparity between the prevalence, awareness, treatment and adequate control of blood pressure amongst the

patients of developing and developed nations, and also between genders (15, 224). This is illustrated in Figure 1.3(15).

Cardiovascular disease is currently the leading cause for mortality worldwide, and especially amongst the Asian population (4, 225). Indians are at more risk of cardiovascular disease, regardless of whether they live in their native lands or overseas (225, 226). Hypertension is one of the major risk factors for mortality within the Indian population (4). Excessive salt intake, alcohol consumption and obesity are the major risk factors (226). Indeed, the mean salt intake is 8.5 grams per day amongst Indians, which is markedly higher than the recommended level (227).

In this study, 63% of the patients had their blood pressure adequately controlled which is still lower than the expected target(100). Unfortunately, there is no huge variation among illiterate and literate, and males and females. Our patients have little knowledge about the importance of adequate control of blood pressure(15, 227) and awareness of complications of hypertension(15). Hypertension is asymptomatic and the measurement of blood pressure is considered as a secondary task by physicians and not routinely employed. Hence, the early diagnosis of hypertension is often overlooked (15). Even for patients receiving treatment for hypertension, there are many reasons for discontinuing the treatment which are listed in Table 6.7. Most common factors are poor awareness, economical burden, the non-availability of drugs, and poor patient-physician interactions (15). Also, treatment guidelines often do not meet the requirements of patients (15).

Overall, awareness regarding hypertension amongst patients is low, which has been persistently and previously reported in the literature (15, 16, 221, 224, 228-230). However, no significant variations between males and females, nor those between rural and urban populations, were observed. This observation may, however, be ascribable to the relatively small sample size (n = 100). There are many studies reported in the literature performed on the Indian population which have demonstrated that the awareness and control rate of hypertension in urban populations is significantly higher than that in rural Indians (12, 16, 99). Potential explanations for this variation could are the relative levels of knowledge, access and availability of treatments (12). However, there are some other studies conducted amongst Indians living overseas which have proven that awareness amongst them was still lacking (231). Unfortunately, many patients were not aware of the serious complications involved (232, 233).

As noted from the observations made here, though there may be small variations regarding hypertension control reports between patients and physicians, the factors responsible for the poor levels of compliance reported by both are similar. Poor patient-physician interactions or relationships are amongst the potential causes for poor compliance (231). Hence, we are aware of what is lacking to achieve adequate disease control; however, further work is required towards that goal in order to improve the standard of care.

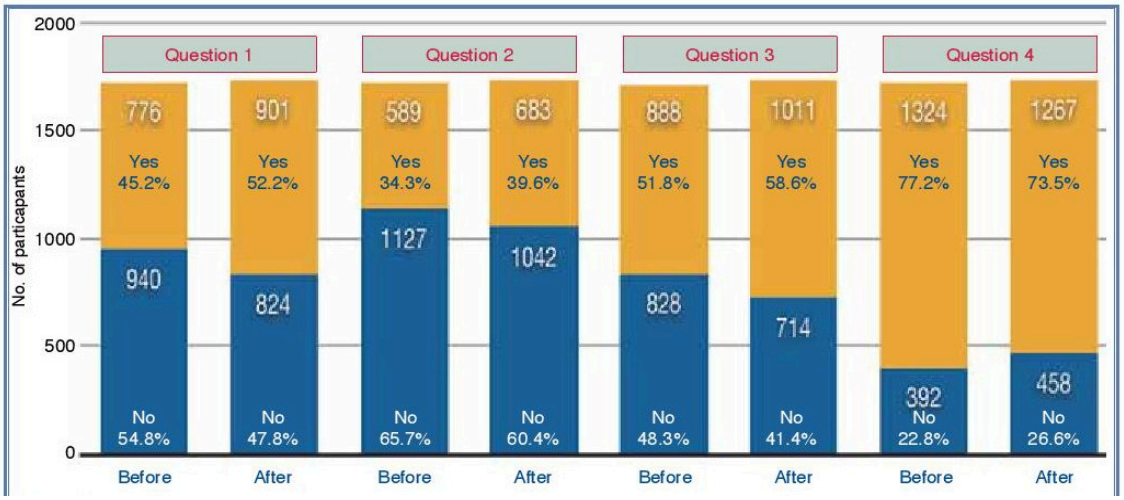
In the PatenT study conducted amongst hypertensive populations in 2003, the prevalence of hypertension was greater in women than men (97). Awareness of the hypertension status amongst the subject group was low, and most of the patients involved had never checked

their blood pressure (the majority of hypertensive patients had inadequate blood pressure control). Interestingly, in this study there was no significant blood pressure difference in the hypertensive patients between the patients who were on pharmacological and non-pharmacological treatments for hypertension (97). The rate of treatment for hypertension and the rate of control of hypertension in Turkey, England, Egypt and USA were 78%, 68%, 60% and 85%, respectively, and 8%, 9%, 8% and 34%, respectively. These results concur with many other survey reports(16, 97).

However, successful initiatives for the management of chronic disease have been performed in a number of developing countries. Indeed, a strong family doctor-based system in Cuba has led to active and early diagnosis, and resulted in significant reductions in the prevalence of cardiovascular diseases; the Cuban healthcare system has the highest rate of controlled hypertension in the world (234). Healthcare workers and community leaders should be trained to promote awareness, and also diagnosis of the disease at an early stage-such participation has been described as successful in many developing countries(235-238). Media and usage of communication devices such as mobile phones and internet services are currently increasing in developing countries. The delivery of messages through such modes is effective, and these represent improved means of controlling chronic diseases such as hypertension and diabetes (98, 239-241). In a study conducted on the Turkish population in order to evaluate the impact of mass media on promoting the awareness of hypertension, there was a significant rise in hypertension awareness amongst the public after mass media campaigns (this is illustrated in Figure 6.1)

(98). This campaign was conducted through television, radio, posters, announcements and also printed materials (98).

Figure 6.1. Graphical demonstration of the percentages of pre- and post-campaign answers based on 'yes' and 'no' responses amongst hypertensive patients



Legend: Figure copied from Oto etal., (98). Question 1: Do you know your blood pressure values?; Question 2: Have you checked your blood pressure within the last 2 months?; Question 3: Do you know the optimal blood pressure levels?; Question 4: Do you know the complications of hypertension?

6.3.1. Patient Empowerment

Patient empowerment is a recent outgrowth in the natural health movement. This provides the patient with an active role in the decision making processes for their own healthcare. Patient empowerment involves patient participation in the awareness programs, communications with doctors and other health care providers, patient safety, evidence gathering, shared decision making, together with discussions with other patients and many others. Empowerment is a multidimensionally complex and contested concept, which

includes a broad social, political, emotional and a emancipatory method (242). Patient empowerment measures include the patient activation measure (PAM) and the patient empowerment scale (PES)(243). PAM estimates the skill, knowledge and confidence of patients in the self-management of health (244). It also predicts patient participation in medical encounters, behavioural change, use of quality behaviours and associated data therefrom (245). PES evaluates the patient's perceived risk and benefits of obtaining access to health and disease (246).

Most of the hypertension awareness programmes focus on the self-empowerment of patients. Hypertension management initiatives conducted in Canada improved the patient's self-empowerment status, and also assisted healthcare providers such as doctors and nurses to manage the hypertension effectively (247).

6.4.Conclusion

A cost-effective public measure to create awareness regarding the prevalence of hypertension amongst the general public is mandatory. Awareness programs should include the provision of information regarding the prevalence, early diagnosis, treatment, control, complications and prevention of this condition, including non-pharmacological approaches (diet and lifestyle modification). Ministries of Health or National societies should promote this awareness through any means of communication such as media, awareness programmes and education at school level (98). Also, there is a major requirement for Governments to provide measures for a legally-acceptable unit of salt in

the processed food available for consumption, such as that currently available in South Africa (248).

A very important consideration regarding disease management in developing countries is to provide effective primary healthcare. Hence, we should take initiatives to strengthen the awareness amongst all healthcare professionals, including nurses and paramedics (249, 250). Though most of the basic drugs in India are provided free of cost, governments should ensure the continuous supply of these drugs in order to maintain an improved level of compliance. All healthcare workers, including physicians, nurses, pharmacists, dieticians, community health and social workers should participate in the control of hypertension. Herculean efforts are therefore required to prevent the epidemic rise in complications, and also stabilise the financial burden arising from these implications.

6.5.Limitations of the study

The limitations of this study include a relatively small sample size, together with many patients not willing to provide their income, and some also not willing to provide their occupational status; hence, socioeconomic status was not assessed. Moreover, all the patients recruited to the investigation were from same geographical region.

CHAPTER 7: GENERAL DISCUSSION AND FURTHER RESEARCH

7.1. Reviewing rationale

Study I : End organ damage in newly detected hypertension

It was observed that 86% of patients who participated in the study had one or more forms of end organ damage ie., microalbuminuria, left ventricular hypertrophy or retinopathy. Unfortunately, all of these patients have had their diagnosis of hypertension only at the time when their end organ damage was first diagnosed. Multiple aetiologies include lack of awareness amongst the general public and physicians not being able to find or exclude secondary causes of hypertension.

Study II: Thyroid disorders and hypertension

We can strongly conclude from study among large number of patients that hypertension (both systolic and diastolic hypertension) is significantly associated with thyroid dysfunction. Interestingly, a new observation that mean arterial pressure and ratio of systolic to diastolic blood pressure are higher among thyroid disorders.

Study III and IV: Awareness among physicians and public

Awareness among health care professionals and public is mandatory for managing the chronic non-communicable disease such as hypertension. A preliminary step in the disease occurrence is the lack of awareness and poor communication. We have noted that awareness among public is well below the expected level. Not only that, knowledge, attitude, behavior and practice of hypertension management among the physicians are sub-optimal.

7.2. Summary and Findings

- The confirmation of powerful relationships between hypertension and end organ damage (EOD) such as retinopathy, microalbuminuria and left ventricular hypertrophy/increased left ventricular mass
- Since all EODs are interdependent, the presence of one or another of these clinical developments mandates the requirement for intensive evaluation
- In cases of snake-bite (prevalent in India), the possibility of severe hypertension requiring oral or intravenous anti hypertensives may be required.
- Systolic hypertension and systo-diastolic hypertension are common in hyperthyroidism and hypothyroidism, respectively
- Significant associations exist between SBP:DBP ratio, MAP and thyroid disease status
- In India, knowledge, attitude, behaviour and practice towards hypertension and its guidelines and management amongst physicians were sub-optimal. These may be improved through clinical governance and CME programs.
- Awareness about hypertension and treatment among general public was well below the satisfactory point. This mandates the urgent need to promote such awareness through media, campaign and social education. Also, it is worthwhile to re-analyze the knowledge about hypertension/its treatment post-awareness program.

7.3. Implications and importance of the findings

1. Regular monitoring of blood pressure along with weight and height in all clinics or during hospital visits, which will enable to detect the diagnosis of hypertension early which in turn prevent the complications
2. Adequate blood pressure control is needed to prevent end organ damage
3. Routine screening for end organ damage in all hypertensive patients is essential to diagnose end organ damage earlier
4. Secondary causes of hypertension need to be considered, and also to be implicated where appropriate; at least in patients with resistant hypertension, hypertension in an unusual age group, severe hypertension, hypertension with end organ damage or any other associated signs of secondary causes
5. Thyroid disorders are common in India, and are increasing in prevalence. Most of the thyroid disorders are undiagnosed in India. It is therefore essential to screen the patients for thyroid dysfunction in all hypertensive patients or at least with one or more of the features suggested 4 above.
6. It is mandatory to enforce and empower the knowledge and awareness regarding hypertension amongst physicians and the general public in order to prevent mortality and morbidity associated with hypertension. Also, it is vital to stabilise the economic burden for the country. Hence, health authorities should promote awareness programs through media or any other modes for the public, and also educate and conduct regular mandatory continuing medical education programs amongst physicians.

7.4. Further research

- Initiate the periodic monitoring of blood pressure in all clinics or hospital visits, and then assess the prevalence and incidence of hypertension, and hypertension with end organ damage, with regard to age, sex, and geographic location (urban or rural), and also assess the associated mortality and morbidity rates, and the overall cost benefit. Since in our study, we found that newly detected/undiagnosed hypertensive patients presented with end organ damage which has further implications.
- Periodic screening of end organ damage in hypertensive patients, including an assessment of the mortality and morbidity benefits with regard to cardiovascular risk factors amongst the Indian population, is considered vital. In India, currently there are no standard guidelines available for the screening of end organ damage in hypertensive patients, and most of them have more than one or other risk factor for such end organ damage. Hence, such screening processes will serve to diagnose these complications at an early stage.
- Thyroid dysfunctions are increasing in prevalence, and hypertension is commonly associated with it. Hence, it is clearly worthwhile to assess the cost effectiveness of screening all hypertensive patients for thyroid dysfunction which will enable us to prevent complications involved. However, further studies are warranted in order to establish the cost-effectiveness of such interventions.

- Thyroid function should improve with adequate treatment(s) for particular disorders (either hormone replacement or anti-thyroid hormone). However, blood pressure will improve in hypertensive thyroid disorder patients, and further studies are required to assess, correlate and estimate values of TSH, T4, and T3 with regard to blood pressure values and end organ damage in hypertensive patients with thyroid dysfunction. Since this will yield more valuable information regarding whether any of the thyroid hormones have relationships with prognostic, mortality, morbidity and treatment responses for hypertension.
- Snake bite is a common problem in India; hence, further studies are required amongst a larger Indian population in order to establish the relationships between blood pressure and snake envenomation, and also the urgent need for early treatment. Because catecholamine surge is one of the pathologies which gives rise to marked blood pressure elevations and increases mortality, early treatment with anti-hypertensive drugs not only controls the blood pressure, but also reduces the catecholamine cascade.
- As noted from this study, physicians KABP are sub-optimal, and most of the physicians require training in many aspects of hypertension. Further studies are therefore required amongst physicians to study KABP after proper training has been given so that their KABP can be evaluated post- training, or respond to desires for further training processes or deficits in the training module delivered; changes in the delivery of such training or training modules should also be considered.

- Knowledge and awareness amongst the general public regarding hypertension are currently lacking. Hence, there is a major requirement to promote the awareness program. More importantly, it is important to study their knowledge and awareness during both pre- and post-campaign/awareness programmes amongst the Indian population, and also to monitor patient activation measures and patient empowerment scales (98).

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APPDENDICES

APPENDIX I - Questionnaire

Appendix I: QUESTIONNAIRE STUDY AMONG PHYSICIANS ABOUT

HYPERTENSION MANAGEMENT

Name (optional):
Specialty (mandatory):
Practice location (village/town): Age (optional): Sex (optional):

1 How many hypertensive patients have you seen in your practice during the past 12 months?

2 How many of these were newly diagnosed hypertensive patients?

3 Please give the percentage distribution of your hypertensive patients according JNC VII crteria
Normal (<120/80) - Pre-hypertension (120-139/80-89) -
Stage I (140-159/90-99) - Stage II (>159/99) -

4 How much time do you spend in seeing a hypertensive patient?

5. Please indicate separately mean time in minutes for
First visit - Therapy titration visits - Follow-up visits –

6. How many visits do you do on average during the first 3 months in order to achieve goal blood pressure?

7. What proportion of your patients is receiving antihypertensive monotherapy?

8. Prefer the drug of choice for HTN (monotherapy), for patients without any evidence of end organ damage/co-existing illness (PLEASE GIVE YOUR ORDER OF PREFERENCE like 1,2,3,4,5,6,7,8,9,)
ACE inhibitor - Angiotensin II receptor antagonist - Beta-blocker –
Ca Ch blocker - Loop diuretics - Thiazide diuretics - Aldosterone antagonist – Alpha blocker - Vasodilator –
Others.....

9. When monotherapy is unsuccessful, what compound do you preferably add to existing monotherapy? Please provide up to three choices in order of preference.

10. What percentage of hypertensive patients in your practice had antihypertensive therapy discontinued or required switching from an antihypertensive compound to another during the past 12 months?

11. How often was therapy discontinuation or switching due to: (please provide %)
a) inadequate blood pressure lowering;
b) side effects of the drugs;
c) availability of newer and better compounds;
d) interaction of the antihypertensive agent with other concurrent therapies;
e) other reasons.....

12. Please indicate the percentage incidence of adverse responses to each of the major classes of antihypertensive agents, in your patients during the past 12 months.

13. Please indicate the predominant type of adverse effect observed in your patients with each of the major classes of antihypertensive drugs.

14. What is your more frequent choice when side effects are observed? (please provide %)
a) Dose reduction of the original compound;
b) switching to another compound;
c) prescription of laboratory examinations;
d) addition of another antihypertensive agent aimed at controlling side effects.
e) others .....

15. What is the preferred class of antihypertensive agent you choose when switching from a compound of each class because of adverse effects?

16. What do you estimate is the percentage of your hypertensive patients who do not comply with your prescriptions?

16 What are the main reasons for patients' poor compliance? (please provide %)
a) Forgetfulness of prescriptions;
b) side effects of drugs;
c) refusal to accept the chronic nature of the disease;
d) lack of understanding of the importance of long-term continuing treatment;
e) complexity of the drug regimen.
f) others .....

17 Which of the following suggestions do you recommend in order to improve compliance? Choose the order of preference like 1,2,3.....
a) dosage simplification;
b) educational interventions and provision of information to the patient;
c) good physician±patient interaction;

d) improved drug efficacy;
e) improved tolerability profile of drugs;
f) single-agent therapy.
g) others.....

18) How many percentage of your hypertensive patients were maintained on diet only?

19) How many percentage of your hypertensive patients have/had one or other end organ damage?

20) Please mention the type and frequency of end organ damage in your patients? (mention in %)

21) How many hypertensive patients attended the counselling/awareness programme on HTN?

22) Did you conduct any awareness programme on HTN?

23) Do you refer your hypertensive patients to dietician?

24) What are the common issues in managing the hypertensive patients in your practise?

25) Do you subject your sphygmomanometer for standardization or check your sphygmomanometer for error?
Yes □ No □
If yes, how frequently…….

26) Are you very much familiar with errors of sphygmomanometer device?
Yes □ No □
If yes, please mention the possible
errors……

27) Please mention the BP cuff size for the following in inches:
Infant…….. Paediatric ……. Normal sized adult…… Obese …….
Formulae or way to find the exact cuff ……

PRACTITIONER'S ATTITUDE TOWARDS THE LEARNING ASPECTS ON HYPERTENSION

Please read everyone and tick appropriate columns as per your need.

Areas of learning/ interest	0	10	20	30	40	50	60	70	80	90	100
1.Historical aspects											
2.Epidemiology											
3.Symptoms											
4.Signs											
5.Clinical evaluation											
6.Investigation											
7.Assessment											
8.Drugs used in practice and future											
9.Adverse effects of drugs											
10. Course and complications											
11.Audit											
12. Issues in pregnancy &lactation											
13. Follow up											
14. Prevention											
15. Traditional practices used											
16. Alternative medicines											
17.Socio-economic aspects											
18. Yoga / meditation											
19. Legal aspects											
20. Patient education											
21. Formulation of standard guidelines for hypertension											

Percentage from 0 to 100 indicates the priority/rank with 0% as least important (not agree) and 100% as most important (strongly agree)

22. Any others, please mention:

THANK YOU SO MUCH FOR YOUR VALUABLE TIME AND RESPONSE

APPENDIX II – Questionnaire

Appendix II: QUESTIONNAIRE SURVEY AMONG PUBLIC ABOUT THE AWARENESS OF HYPERTENSION

Dear friend

We are conducting a study to find out the awareness of hypertension. As you have high blood pressure (BP) we would like to collect some information on your views related to the medication(s) consumed for blood pressure, test carried out and bad effects of medicines taken for high blood pressure. Kindly read each questionnaire / Statement and respond to each in the respective column. Your participation is greatly appreciated, as your information will help us to plan our educational programmes for practitioners. Your name and identity will not revealed to third party members.

Thank you very much for your valuable participation

Name : Domicile (village /Town)……

Age : Educational status……

Gender: Record No: OP/ IP ……

Date Occupation……..Income per month…….

No	Questionnaire / statement	Yes	No	Comments
1.	Do you ever had high blood pressure (BP)?. If yes, what was your age at the time of diagnosis as high blood pressure (BP) ? Mention here…….			
2.	Did the Doctor or Nurse tell you that you have high BP?			
3.	Are you taking medicines for high BP, if yes?			
4.	How long are you taking medicines for high BP ---------- ----- years / …..Months			
5.	Do you still have high BP ?			
6.	Kindly mention the name of the tablets taken for high BP? ……..			
7.	When did you check your BP? 12 month ago ☐ 6 month ago ☐ Kindly let me known the date			
8.	What did they tell you when your BP was recorded? Normal Under control High…… What was the level? Mention if you know…….			
9.	Do you have BP recording machine at home? If yes, Mention the name of the machine……			
10.	Do you check BP on your own?			
11.	Have you ever stopped taking medicine for high BP?			

	If yes why? 1. Bp is not getting controlled ☐ Forgotten to buy tablets ☐ No symptoms ☐ BP under control ☐ No belief in medicines given for high BP ☐ Any other – specify ☐			
12.	Are you following any methods to reduce high BP? If yes what methods... Weight reduction ☐ Salt reduction ☐ Diet reduction ☐ Smoking ☐ Stop drinking alcohol ☐ Regular BP Checking ☐ Any other specify ☐			
13.	How did you know the effects of about high BP? If yes, how?……. Through Pictures / posters ☐ Through TV …….☐ Through Radio …….☐ Through Books …….☐ Through News papers …….☐ Through Advertisement …….☐ Through Doctors / Nurses …….☐			
14.	What type of food reduces high BP? Food with low salt …….☐ Food with high salt content……. ☐ Food with excessive fat…… ☐ High Fibre diet……☐ Drinking excessive water …….☐ Vegetables and Greens ……..☐ Diet / control Any other specify			
15.	What the alternative ways BP shall be reduced? Peace of mind ……☐ Avoid anger…….☐ Stress…….☐ Yoga ……..☐ Meditation ……☐ Eating Fish …….☐ Any other specify			
16.	Are you aware of adverse effects of HIGH Bp? If yes Heart attack Stroke			

	Bleeding in the brain Kidney failure Sub conjunctival hemorrhage Damage to blood vessels Any other specify			
17.	For woman: During your pregnancy, did any one tell you that you have high B.P?			
18.	Are you suffering from high BP even before pregnancy?			
19.	For all: kindly give your opinion /views on high BP			

20. Any other comments – please mention

APPENDIX III – Institutional Ethical Committee Approval Letters for the studies

CHENNAI MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
(SRM)
[Affiliated to The TN Dr. MGR Medical University, Chennai]
IRUNGALUR, TIRUCHIRAPALLI – 621 105, TAMILNADU

Ref. No: CMCH&RC/IEC–No:09 /12.04.2010

Sub: Approval of research work related to / project of faculty- IEC – Issued-Reg.

The research proposal submitted by Dr Meenakshi Sundaram Ramachandran under the guidance of Dr. P.Thirumalikolundusubramanian Professor of Medicine,Chennai Medical College Hospital and Research Centre, Tiruchirapalli, was discussed and analyzed by the Institutional Ethics Committee of the CMCH&RC. The committee approved the research project subject to existing rules and regulations.

Title of the Research work/Project:

"Status of End Organs in Newly Detected Rural Essential Hypertensive's A Study from Southern India "

a. He should abide to the Ethical aspects of the institutional Ethics Committee.
b. He should not deviate from the proposal submitted
c. He has to inform IEC if any deviation / modification whenever considered.
d. He should carry out the project within the stipulated period and if extension needed, he has to inform IEC.
e. He should get appropriately designed informed consent subjects/patients of the study group.
f. He should not claim any monetary support from IEC
g. He should cooperate with the members of IEC while they visit / monitor the activities.
h. He should entitle to make use of this approval letter for obtaining financial support from funding agencies by submitting his application through the Dean, CMCH&RC.
i. He is informed that he should submit the summary of the report to the IEC after completion of his project.
j. **IEC Comments: Approved**

P. Rajen

Member Secretary

[Dr. P. Rajendran]

Member Secretary
INSTITUTIONAL ETHICS COMMITTEE

To Dr Meenakshi Sundaram Ramachandran through Dr. P.Thirumalikolundusubramanian Professor of Medicine , Chennai Medical College Hospital and Research Centre, Tiruchirapalli.
Copy to Office file.

INSTITUTIONAL ETHICS COMMITTEE ★
Chennai Medical College Hospital & Research Centre Irungalur, Trichy-621 105
Date. 12.4.2010

CHENNAI MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
(SRM)
[Affiliated to The TN Dr. MGR Medical University, Chennai]
IRUNGALUR, TIRUCHIRAPALLI – 621 105, TAMILNADU

Ref. No: CMCH&RC/IEC–No:61 /06.02.2012

Sub: Approval of research work related to / project of faculty- IEC – Issued-Reg.

The research proposal submitted by Dr Meenakshi Sundaram Ramachandran under the guidance of Dr. P.Thirumalikolundusubramanian Professor of Medicine,Chennai Medical College Hospital and Research Centre, Tiruchirapalli, was discussed and analyzed by the Institutional Ethics Committee of the CMCH&RC. The committee approved the research project subject to existing rules and regulations.

Title of the Research work/Project:

"Severe hypertension on Elapid Envenomation"

a. He should abide to the Ethical aspects of the institutional Ethics Committee.
b. He should not deviate from the proposal submitted
c. He has to inform IEC if any deviation / modification whenever considered.
d. He should carry out the project within the stipulated period and if extension needed, he has to inform IEC.
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i. He is informed that he should submit the summary of the report to the IEC after completion of his project.
j. **IEC Comments: Approved**

P. Raj
Member Secretary
Member Secretary
INSTITUTIONAL ETHICS COMMITTEE
[Dr. P. Rajendran]

To Dr Meenakshi Sundaram Ramachandran through Dr. P.Thirumalikolundusubramanian Professor of Medicine , Chennai Medical College Hospital and Research Centre, Tiruchirapalli.

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INSTITUTIONAL ETHICS COMMITTEE
Chennai Medical College Hospital & Research Centre
Irungalur, Trichy-621 105
Date...6/2/2012

CHENNAI MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
(SRM)
[Affiliated to The TN Dr. MGR Medical University, Chennai]
IRUNGALUR, TIRUCHIRAPALLI – 621 105, TAMILNADU

Ref. No: CMCH&RC/IEC–No:67/06.12.2011

Sub: Approval of research work related to / project of faculty- IEC – Issued-Reg.

The research proposal submitted by Dr Meenakshi Sundaram Ramachandran under the guidance of Dr. P.Thirumalikolundusubramanian Professor of Medicine,Chennai Medical College Hospital and Research Centre, Tiruchirapalli, was discussed and analyzed by the Institutional Ethics Committee of the CMCH&RC. The committee approved the research project subject to existing rules and regulations.

Title of the Research work/Project:

"Thyroid disorder and hypertension"

a. He should abide to the Ethical aspects of the institutional Ethics Committee.
b. He should not deviate from the proposal submitted
c. He has to inform IEC if any deviation / modification whenever considered.
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i. He is informed that he should submit the summary of the report to the IEC after completion of his project.
j. **IEC Comments: Approved**

P. Raja

Member Secretary

[Dr. P. Rajendran]

Member Secretary
INSTITUTIONAL ETHICS COMMITTEE

To Dr Meenakshi Sundaram Ramachandran through Dr. P. P.Thirumalikolundusubramanian Professor of Medicine , Chennai Medical College Hospital and Research Centre, Tiruchirapalli.

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INSTITUTIONAL ETHICS COMMITTEE
Chennai Medical College Hospital & Research Centre Irungalur, Trichy-621 105
Date 6/12/2011

CHENNAI MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
(SRM)
[Affiliated to The TN Dr. MGR Medical University, Chennai]
IRUNGALUR, TIRUCHIRAPALLI – 621 105, TAMILNADU

Ref. No: CMCH&RC/IEC–No:74/05.09.2012

Sub: Approval of research work related to / project of faculty- IEC – Issued-Reg.

The research proposal submitted by Dr Meenakshi Sundaram Ramachandran under the guidance of Dr. P.Thirumalikolundusubramanian Professor of Medicine,Chennai Medical College Hospital and Research Centre, Tiruchirapalli, was discussed and analyzed by the Institutional Ethics Committee of the CMCH&RC. The committee approved the research project subject to existing rules and regulations.

Title of the Research work/Project:

"Awareness of hypertension among practicing physicians"

a. He should abide to the Ethical aspects of the institutional Ethics Committee.
b. He should not deviate from the proposal submitted
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d. He should carry out the project within the stipulated period and if extension needed, he has to inform IEC.
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j. **IEC Comments: Approved**

P. Raja
Member Secretary
[Dr. P. Rajendiran]
Member Secretary
INSTITUTIONAL ETHICS COMMITTEE

To Dr Meenakshi Sundaram Ramachandran through Dr. P.Thirumalikolundusubramanian Professor of Medicine , Chennai Medical College Hospital and Research Centre, Tiruchirapalli.

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INSTITUTIONAL ETHICS COMMITTEE
Chennai Medical College Hospital & Research Centre
Irungalur, Trichy-621 105
Date 5/9/12

CHENNAI MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
(SRM)
[Affiliated to The TN Dr. MGR Medical University, Chennai]
IRUNGALUR, TIRUCHIRAPALLI – 621 105, TAMILNADU

Ref. No: CMCH&RC/IEC–No:76/05.09.2012

Sub: Approval of research work related to / project of faculty- IEC – Issued-Reg.

The research proposal submitted by Dr Meenakshi Sundaram Ramachandran under the guidance of Dr. P.Thirumalikolundusubramanian Professor of Medicine, Chennai Medical College Hospital and Research Centre, Tiruchirapalli, was discussed and analyzed by the Institutional Ethics Committee of the CMCH&RC. The committee approved the research project subject to existing rules and regulations.

Title of the Research work/Project:

"Awareness of hypertension among public"

a. He should abide to the Ethical aspects of the institutional Ethics Committee.
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d. He should carry out the project within the stipulated period and if extension needed, he has to inform IEC.
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j. **IEC Comments: Approved**

P. Rajendran
Member Secretary
[Dr. P. Rajendran]
Member Secretary
INSTITUTIONAL ETHICS COMMITTEE

To Dr Meenakshi Sundaram Ramachandran through Dr. P.Thirumalikolundusubramanian Professor of Medicine , Chennai Medical College Hospital and Research Centre, Tiruchirapalli.

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INSTITUTIONAL ETHICS COMMITTEE
Chennai Medical College Hospital & Research Centre
Irungalur, Trichy-621 105
Date 5/9/2012

APPENDIX IV – Publication I